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INNERVATION AND "TONUS" OF STRIATED MUSCLE IN MAN

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Striated muscle is normally under a constant slight mechanical tension even when at rest and removed from the influence of gravity. This is shown by the fact that it contracts—to some extent even in the cadaver—when its tendon is severed. Also, contractures develop in otherwise healthy muscles after their antagonists have been out of function for a while.

An increase of tension beyond what is seen at rest is noticeable in muscles or muscle groups serving to maintain posture, as in standing, without obvious movement.

Resistance to passive movement, of varying degree in normal subjects and in patients suffering from a number of motor disorders, and stiffness of voluntary movement, experienced by patients suffering from "spasticity" and "rigidity," illustrate possibly another form of tension in the muscle.

All these various states of tension, obviously related in some fashion, and such unrelated states as turgor of tissues have been called "tonus." The same term, however, has also been used indiscriminately for the presumable mechanism by which muscular tension is regulated and adjusted. Especially in the clinical literature, there has always been a certain amount of disagreement concerning the meaning and definition of tone, in spite of the fact that as early as 1833 Hall [1] had an excellent understanding of the significance of "tonus, equilibrium and reflex-action" in their relation to the spinal medulla.

Hypertonia and hypotonia of the musculature, dystonia, "tonic" seizures, etc., are important clinical concepts, and their relation to "tonus" might well be analyzed. The purpose of this study is to deter-

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1. Hall, M.: On the Reflex Function of the Medulla Oblongata and Medulla Spinalis, Philos. Tr. Roy. Soc., London **123**:635, 1833.

mine how much of the tension of striated muscle [2] in man in health and in disease is regulated by nerve impulses. Toward this end two assumptions have been made: first, that whenever nerve impulses are effective in striated muscle, action potentials can be recorded from the muscle, and, second, that the action potentials of striated muscle are discharges of motor units and that no other form of motor innervation exists. Both assumptions will be discussed later.

MATERIAL AND METHODS

Observations were made on muscles of normal subjects and those of patients suffering from various neurologic diseases. They were examined at rest, during active and passive movement, during postural activity and during involuntary movement. Potentials were recorded from single muscles and simultaneously from antagonist pairs of muscles or from any number (up to six) of muscles presumably involved at the same time. In order to obtain a picture of the gross total of impulses reaching a muscle, flat surface electrodes were used, while coaxial needle electrodes were employed when single or small groups of motor units were to be studied. The recording instruments—cathode ray oscillograph and multichannel ink-writing oscillographs—have been described in detail elsewhere.[3] The material has been collected during the past four years, and some of the observations have already been published.[4]

RESULTS

Normal Muscle.—No indication of innervation as postulated here was found in normal muscle at rest in subjects who were able to relax voluntarily. A number of records are presented in figure 1. They were taken from the biceps, the triceps, the extensor and flexor muscles of the wrist, the rectus femoris, the tibialis anticus and the gastrocnemius. Both coaxial needle electrodes and surface electrodes were used. In all instances the tracings were obtained from the muscles at rest and during voluntary innervation. With the onset of activity unmistakable diphasic action potentials were recorded, in contrast to the electrical inactivity of the "base line." In *C* to *F* of figure 1 the relation of two pairs of antagonists is shown during simple voluntary movement of first one and then the other muscle. In *C* and *D* no activity is recorded from the antagonist during powerful innervation of the protagonist, while in *E*

2. "Tonus" of smooth muscle, as it is exhibited, for example, in the innervation of the bladder, has not been part of this investigation, and none of the conclusions reached here ought to be interpreted for anything but striated muscle.

3. Hoefer, P. F. A., and Putnam, T. J.: Action Potentials of Muscles in Normal Subjects, Arch. Neurol. & Psychiat. **42**:201 (Aug.) 1939.

4. Hoefer, P. F. A., and Putnam, T. J.: (*a*) Action Potentials of Muscles in "Spastic" Conditions, Arch. Neurol. & Psychiat. **43**:1 (Jan.) 1940; (*b*) Action Potentials of Muscles in Rigidity and Tremor, ibid. **43**:704 (April) 1940; (*c*) Action Potentials of Muscles in Athetosis and Sydenham's Chorea, ibid. **44**:517 (Sept.) 1940; (*d*) Electromyographic Studies of Normal and Abnormal Movement, Tr. Am. Neurol. A. **65**:18, 1939.

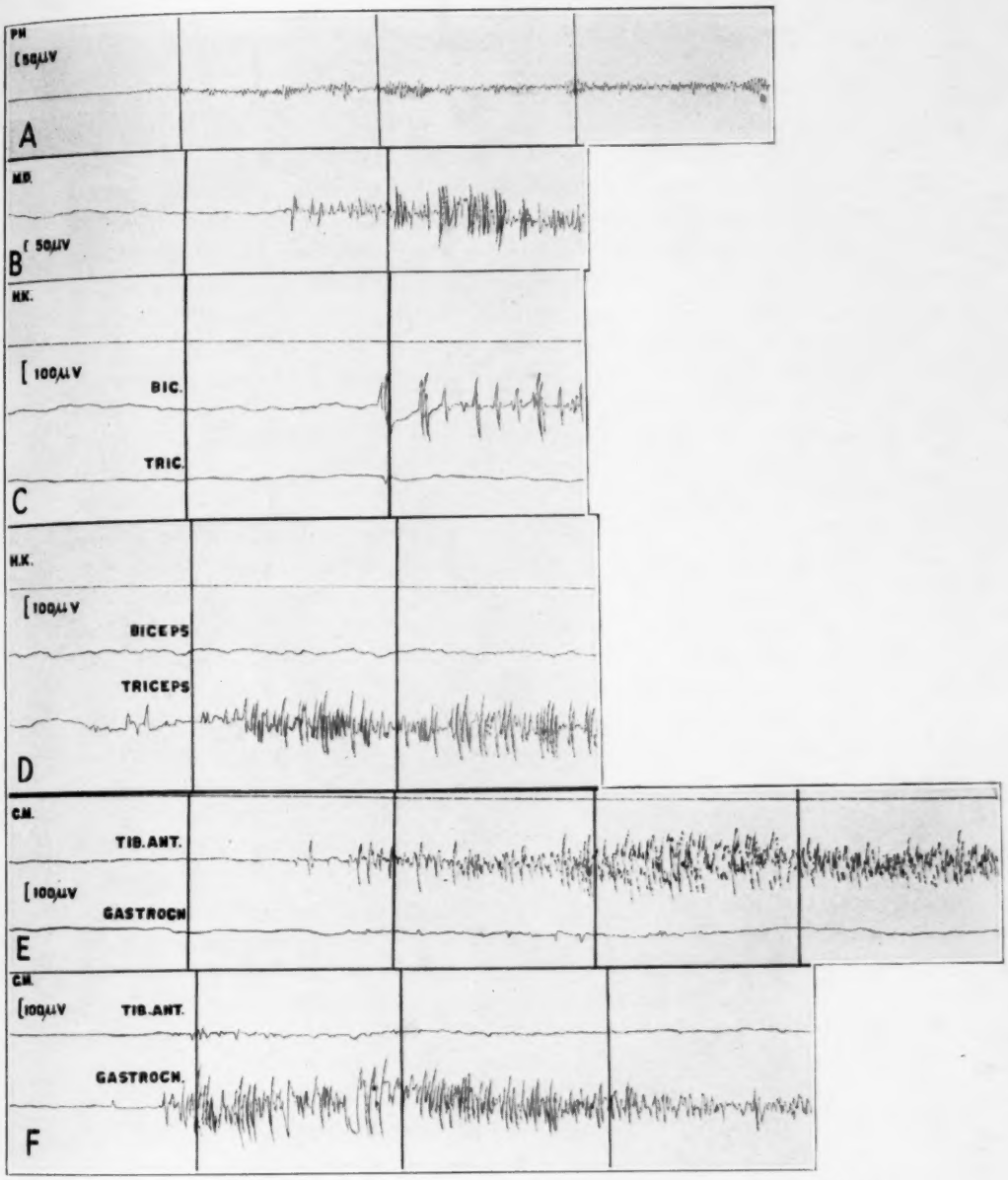

Fig. 1.—Normal muscle in man, at rest and with onset of movement. Ink-writing oscillograph. Time: one second between vertical lines. Calibration marked on each record.

A: Rectus femoris; coaxial pair of needle electrodes.

B: Extensor group of forearm; surface electrodes.

C: Simultaneous surface leads from biceps and triceps; moderately strong flexion.

D: As in *C*, but during extension.

E: Simultaneous surface leads of tibialis and gastrocnemius; powerful dorsiflexion.

F: As in *E*, but during plantar flexion.

and *F*, with maximal innervation, a small amount of activity is seen in the lead from the antagonist.

It has been shown by Sherrington [5] that antagonists relax while protagonists contract in response to stimulation of the motor cortex. The question how far it might be permissible to extend the concept of "reciprocal innervation" to the voluntary innervation of single muscle in normal subjects will be discussed later. The situation with respect to passive movement of normal muscle, however, is entirely different, and nothing like "reciprocal innervation" should be expected with it. Here a lengthening of the muscle opposed to the movement should be expected, with increase of tension instead of relaxation. The response of normal muscle to this type of stretching depends largely on the speed at which the change is made, as well as on the final change in length produced and the angle to which the joints are brought. It is possible in most normal subjects to carry out passive flexion and extension within certain variable limits of speed and range without causing any electrical response in the muscles moved. Above a certain rate of speed, which varies with different subjects, action potentials begin to appear, usually with some delay. In figure 2 a number of observations of this kind are presented in the order of events. In the first record (fig. 2 *A*) slow passive movements of a pair of antagonist muscles, extensor and flexor of the wrist, are shown in simultaneous surface leads, in which no indication of activity is found. In the next records (fig. 2 *B* to *D*) the passive movement is increasingly faster and more extensive. The tracings show at first a few action potentials in the stretched muscle alone, low in voltage and far apart, indicating that only a few units at a time take part in a long spreading-out stretch response. Next, a greater number of potentials is recorded from the stretched muscle during approximately the same length of time, and, usually with a delay of a few seconds, potentials are also seen in the antagonist of the stretched muscle. Next, the response becomes shorter while the individual spikes become larger, indicating that a larger number of units are discharging at the same time. The last record, obtained in response to very brisk stimulation, shows a single large spike indistinguishable from a proprioceptive reflex action potential, the "envelope" of a synchronous, or almost synchronous, volley from the active motor units. The response in the antagonist to the stretched muscle is occasionally, but not invariably, seen when the movement begins to be painful, or at least unpleasant. In some other observations, especially when records were taken from the calf musculature and

5. Sherrington, C. S.: (*a*) The Integrative Action of the Central Nervous System, New York, Oxford University Press, 1920; (*b*) On Reciprocal Innervation: The Co-ordination of Antagonists, in Selected Writings of Sir Charles Sherrington, edited by D. Denny-Brown, New York, Paul B. Hoeber, Inc., 1939, chap. 7, pp. 237-313.

the tibialis anticus, no response was found until the synchronous single reflex discharge occurred (fig. 2 *E*).

The action of muscles serving to maintain posture, for example in standing, appears to be infinitely more complicated, and at first sight it

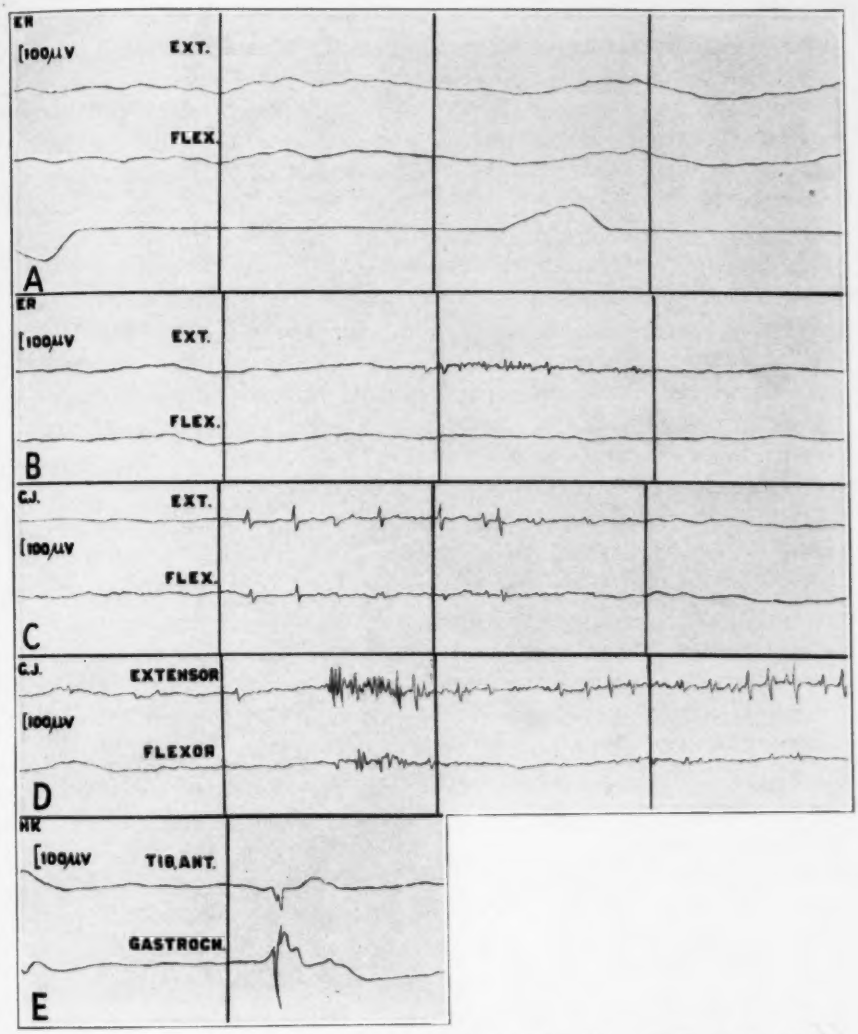

Fig. 2.—Normal muscle in passive movement. Ink-writing oscillograph. Time: one second between vertical lines. Calibration marked on each record.

A: Slow movement without response.

B, C and *D:* Increasing rate of movement with increasing response first in stretched muscle, later also in antagonist.

E: Single response resembling tendon jerk.

would seem impossible to obtain a true picture of the innervation involved. Some pertinent information, however, can be gathered in a

simple manner, namely, from observation of the calf (gastrocnemius) and the tibialis muscle alone. This pair of muscles, acting as synergists in standing, serves to fix the ankle joint and, by adaptation of its angle to the swaying of trunk and thighs, carries at times a good deal of the entire weight of the body. A series of observations on two normal subjects standing under varied conditions is presented in figure 3. The first records (*A* and *B*) were taken from a female subject standing at perfect ease on both feet. The electrodes were placed on the skin over the left tibialis and gastrocnemius muscles, the left leg being the dominant one. Figure 3 *A* shows hardly any activity in either muscle; in *B* a moderate amount of activity in the tibialis is seen, while the lead from the gastrocnemius shows none now or at any other time during this recording. The two next records (*C* and *D*) were taken while the same subject was standing on the left foot alone. In this part of the observation both muscles were continuously active in varying degree, but again there was less activity in the calf musculature. It is interesting to note that the same distribution of activity was seen in 2 other female subjects, while the reverse was observed in 4 normal male subjects. Figure 3 *E* and *F* are from two of the last observations on a male subject standing on both legs and on one leg alone, respectively. While for the normal subject standing on both legs is almost effortless, with only a slight amount of swaying, standing on one leg requires a great deal of balancing, and coarse swaying movements were seen in all instances.

Spasticity and Rigidity.—A number of observations on the behavior of striated muscle in spasticity and rigidity have been reported recently.[6] New observations have confirmed the previous ones, and it may therefore be sufficient to summarize here the results concerning the electrical activity during rest and in response to passive movement.

"Spastic" muscle at rest is not in spasm but is relaxed. It is, however, not always easy to find a position of rest for it. Tension produced by faulty placement or by gravity or sensory stimuli not effective in a normal subject may produce a reflex contraction which under certain conditions spreads widely in a fashion only partly predictable.

In figure 4 a number of observations on patients with moderate spasticity are shown. The first record (*A*) is taken from the rectus femoris muscle with three pairs of coaxial needle electrodes. It shows the muscle at rest, without any sign of basic or "tonic" activity, and the onset of voluntary movement, with the tendency to synchronous motor unit discharges considered characteristic for the physiologic state of "spasticity,"[4a] as defined previously. The next records are taken from another patient with surface leads placed over the biceps and triceps. Figure 4 *B* shows the muscles at rest. Slow passive flexion of the arm, which has no effect on normal muscle, produces here (*C*) a marked

6. Hoefer and Putnam (footnote 4 *a* and *b*).

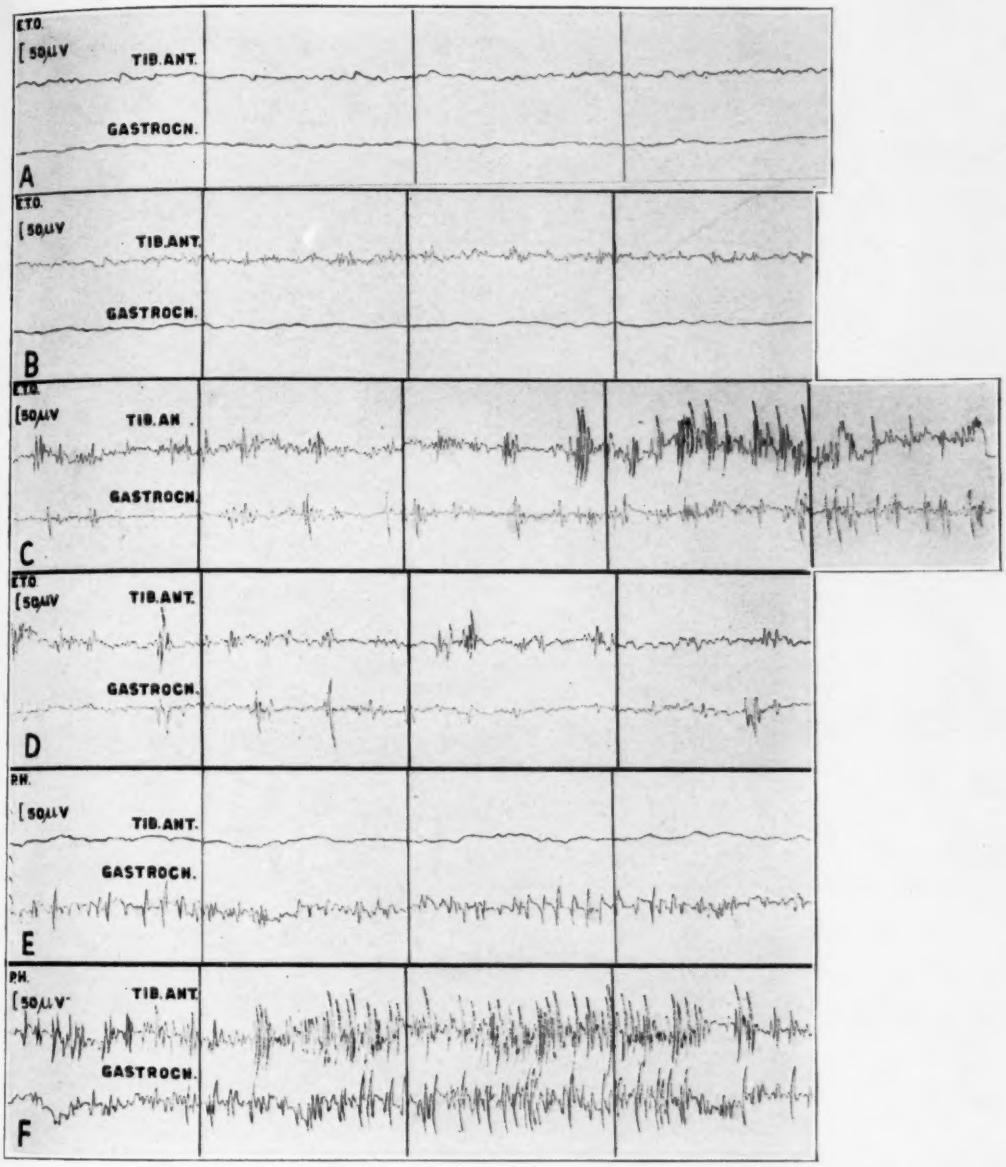

Fig. 3.—Normal subjects standing. Surface electrodes on tibialis anticus and gastrocnemius. Ink-writing oscillograph. Time: one second between vertical lines. Calibration marked on each record.

A: Subject standing at ease, on both legs.

B: Same subject, some activity in tibialis muscle.

C and *D:* Same subject standing on one leg alone in two different phases of balancing.

E: Second subject standing on both legs. Note activity in calf muscles only.

F: Same subject as in *E* standing on one leg alone.

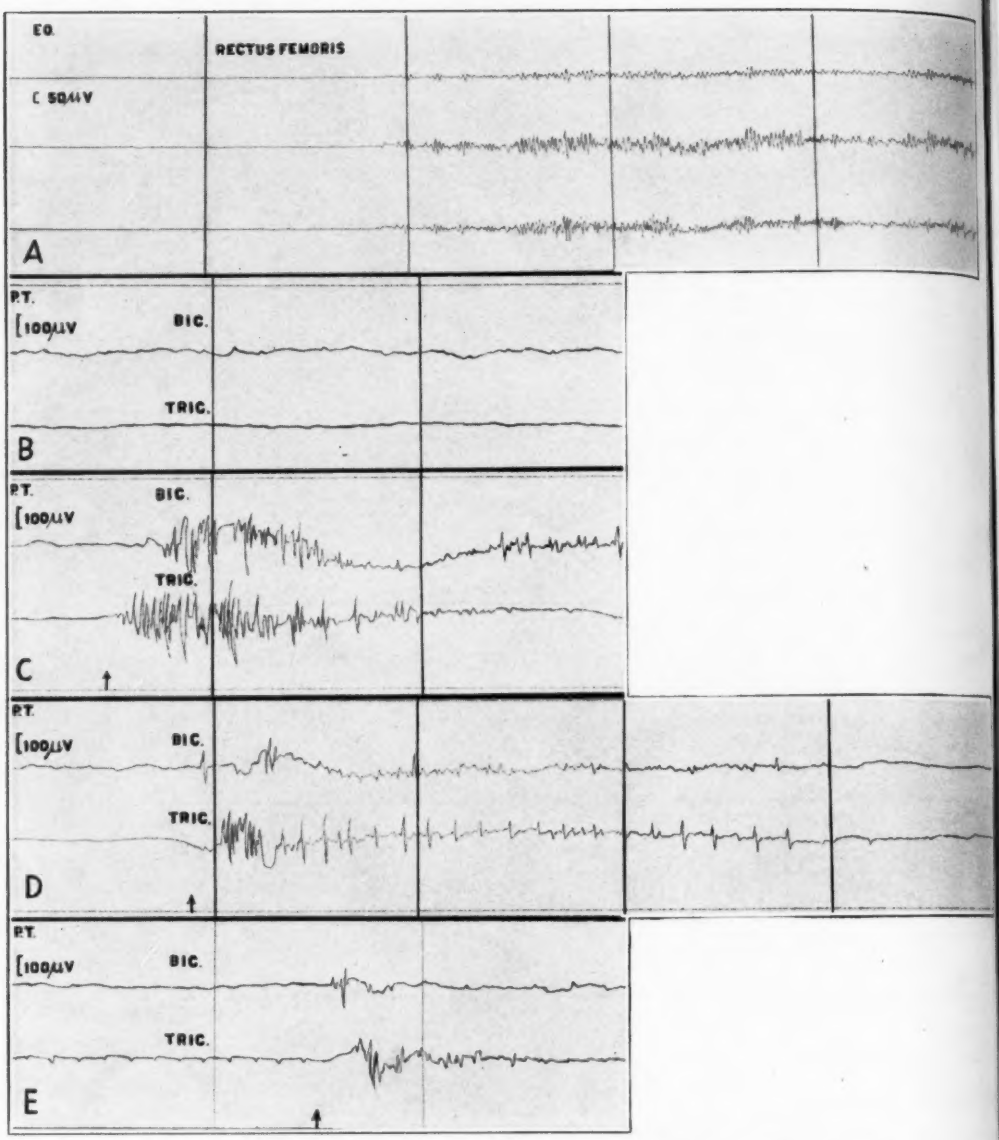

Fig. 4.—Spastic muscles at rest and in active and passive movement. Ink-writing oscillograph. Time: one second between vertical lines. Calibration on each record.

A: Rectus femoris at rest and during onset of voluntary movement; three coaxial pairs of needle electrodes.

B: Simultaneous records from surface leads on biceps and triceps at rest.

C: Simultaneous records from surface leads on biceps and triceps, showing response to slow flexion, i. e., stretching of triceps. Note quiet "base line"; response first in triceps, then in biceps.

D: As in *B,* but with slightly more brisk passive flexion. Note almost simultaneous responses in both muscles; no activity while at rest.

E: Same as in *B* and *C,* but with slow extension. Note reversed sequence of events.

response, first in the muscle stretched, namely, the triceps, and, with a delay of about two-tenths second, an even more marked response in the biceps. A slightly more brisk passive flexion, which is still ineffective in most normal subjects, produces a powerful, almost simultaneous, response in both muscles (*D*), and, finally, passive extension is shown which at slow speed of motion produces a similar effect (*E*), first in the biceps and, with a delay, in the triceps. In all these records (fig. 4 *B* to *E*) the complete electrical inactivity of the muscles before the movements should be noted.

In cases of rigidity, both of Parkinson's disease and, in 1 instance, of human decerebrate rigidity, a constant low voltage activity was found

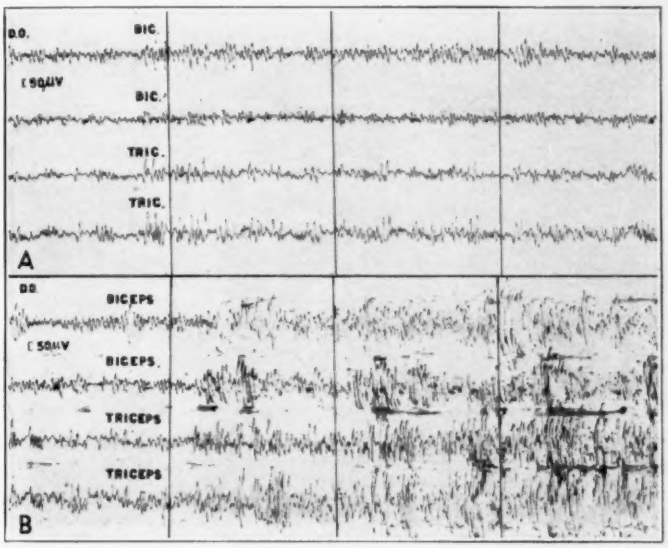

Fig. 5.—Muscles in rigidity at rest and in passive movement. Ink-writing oscillograph. Time: one second between vertical lines. Calibration marked on each record. Biceps and triceps, with two pairs of coaxial needle electrodes in each muscle.

A: At rest.

B: Passive flexion.

in the muscle "at rest," under conditions in which in cases of spasticity no activity was found. With passive movement, however, a response very similar to that in spasticity was noted, i. e., a marked response to stretch with secondary response in the antagonist muscle. The similarity in the response to passive and active movement in the two conditions has been discussed in detail,[4b] and the mechanism responsible for the similar behavior has been concluded to be the same. Active movement carried out by the patient stimulates the antagonist by stretching

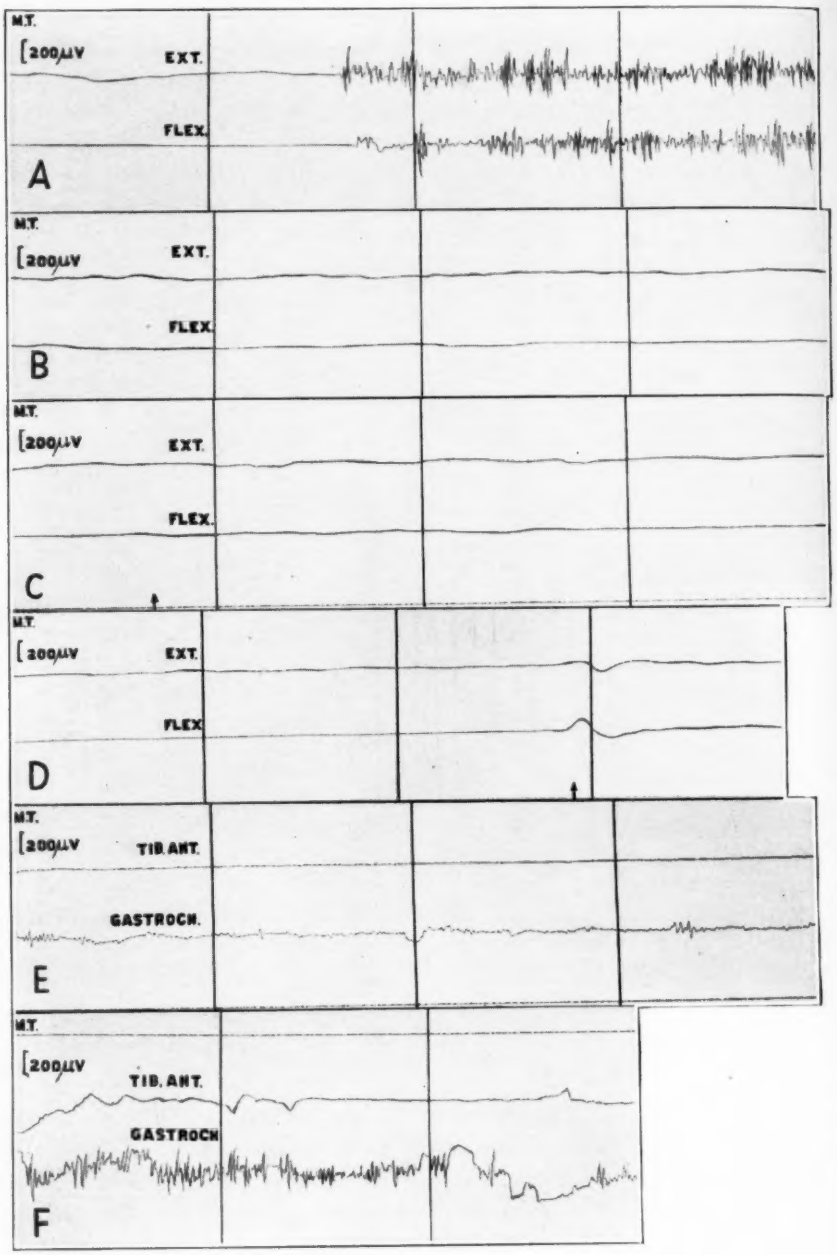

Figure 6

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and amounts to passive movement of the latter. In figure 5 two records are shown, one of two "rigid" antagonist muscles at rest and one of the same pair of muscles during onset and the first second of passive movement. In this instance, two pairs of coaxial needle electrodes were inserted into each muscle, and simultaneous records of all four motor unit groups were taken.

Hypotonia Associated with Cerebellar Dysfunction.—A number of patients were studied in whom tumors of the cerebellum or of the cerebellopontile angle had been removed some time prior to the observation. All of them showed hypotonia and most of them ataxia as well. Some were still ill and could be subjected to only a few tests—for example, the recording from muscles during active and passive movement—but several were able to stand at least for a while. All the patients examined had good muscular function, as tested by the hand grip, by making a fist or by pressing the foot down. No activity was seen in resting muscle. Several observations recorded on 1 patient are presented in figure 6. The first record (*A*) is taken from the extensor and flexor groups, respectively, of the wrist. The first half of the record shows the muscle at rest; the last part shows the beginning of a powerful voluntary innervation. The next three records (*B* to *D*) show, respectively, the result of slow passive extension, slow passive flexion and quick passive extension. In all instances the movement was carried out to an extreme angle of much more than 90 degrees. The patient felt no pain. In no instance was a muscle potential recorded. The slow shift of the base line in *D* is a mechanical artefact produced by the movement. The last two records, *E* and *F*, were taken from the tibialis anticus and the gastrocnemius while the patient was standing with some support, first on both legs (*E*) and then on the hypotonic leg alone (*F*). These last two records are not essentially different from those obtained from normal subjects under the same conditions.

The patients of this group were selected because they showed the cerebellar symptoms in as pure a form as possible, especially without

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EXPLANATION OF FIGURE 6

Hypotonia of muscles caused by cerebellar dysfunction. Ink-writing oscillograph. Time: one second between vertical lines. Calibration marked on each record.

A: At rest and onset of voluntary innervation. Surface electrodes on extensor group (upper tracing) and flexor group of the wrist.

B: As in *A*, but during slow passive extension carried out to extreme angle.

C: As in *B*, but during slow flexion.

D: As in *B*, but during quick flexion.

E: Standing on both legs with support. Surface electrodes on tibialis anticus and gastrocnemius.

F: As in *E*, but while standing on one leg alone.

any appreciable spastic component. Two additional patients were seen for whom the diagnosis of cerebellar tumor was unverified. One of them showed marked hypotonia and ataxia; the other, who was studied more than eight weeks after operation, gave essentially normal responses to passive movements.

Athetosis, Dystonia and Chorea.—In a previous report [4c] it was shown that in spite of a wide difference in the etiology and course of the underlying diseases and notwithstanding a great variety in the appearance of the involuntary movements, the three conditions have a number of features in common. These are the irregular, more or less sustained simultaneous innervation of antagonist muscle groups, in "abrogation of the law of reciprocal innervation," as Kinnier Wilson [7] put it,[8] and the asynchronous management of motor units of the individual muscle, resembling that in voluntary activity and essentially different from the tendency to synchronization of motor unit discharges found in spasticity and rigidity.

It is customary in many clinics to distinguish between athetosis and dystonia on purely descriptive grounds. It is usually accepted that the movements of athetosis are on the whole slow and irregular and occur in the distal parts of the limbs. In dystonia the muscles of the trunk, neck and head are said to be chiefly involved. The movements here repeat certain slow patterns, and, furthermore, distortions and fixations of the body, sometimes in fantastic postures, rather than active movements, often occur. Oppenheim,[9] who, among the first, described and named "dystonia musculorum deformans," had suggested the term "dysbasia lordotica progressiva" as an alternative. There is yet no general agreement, however, as to the differential diagnostic points. Grinker [10] described the movements of dystonia as "similar to athetosis," and Kinnier Wilson, in his new textbook,[11] stated that "double athetosis" is a "purely symptomatic term" and that "torsion-spasm [dystonia] seldom occurs by itself, distinct from allied syndromes or diseases such as chorea, athetosis, parkinsonism, lenticular degeneration . . ." It is "hardly anything else than a variety of athetosis, proximal rather than distal." It is often stated that "tonus" is diminished in chorea, while in athetosis and dystonia there are rapid changes from hypertonia to hypotonia. Another frequent statement is that in dystonia the innerva-

7. Wilson, S. A. K.: Modern Problems in Neurology, London, Edward Arnold & Co., 1928.

8. The validity of this statement is questionable, at least for involuntary movements, as will be discussed later.

9. Oppenheim, H., cited by Wilson.[11]

10. Grinker, R. R.: Neurology, ed. 2, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

11. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940.

tion is "tonic" because the muscles are often under tension without movement. It has been pointed out before [4c] that in the hyperkinetic states it is almost impossible to distinguish active, passive and involuntary movements, because the patients while being examined move more frequently and violently and also because the electrical patterns of voluntary and involuntary movements are so similar.

No attempt, therefore, will be made to present and interpret the results of passive movement in athetosis and the other dyskinetic states. It is possible, however, to observe a number of features of clinical significance and to throw light on the question of "tonic" innervation by means of studies of the action potentials recorded in involuntary activity.

Six observations on 3 patients are presented in figure 7. They were taken from a patient (G. S.) who belonged to the dystonia group, from a second patient (M. D.) whose case clinically was clearly one of athetosis and from a third patient (F. B.) who showed the features of both disorders (as do most of the patients whom my associates and I have studied). In all 3 instances electrical inactivity was seen at times either in leads from single muscles or in leads from motor units, or even in all leads simultaneously. This is always seen when there is no movement or tension of the muscle under observation; conversely, whenever the muscles relax no action potentials are recorded. This is clearly seen in the records *A, C* and *E* of figure 7, while in the other three records (*B, D* and *F*) tracings from the same muscles or motor units are shown during involuntary movement. *A* and *B* are records taken from the patient showing "dystonia." Surface electrodes were placed on the left sternocleidomastoid muscle, on the right biceps and triceps and on the flexor and extensor groups of the wrist. The first record (*A*) was taken when the patient was as relaxed as it was possible to find him, and for short periods, interrupted here and there by minimal electrical activity, his muscles were completely quiet clinically as well as electrically. In the next record (*B*) tracings from the same patient are shown during a violent, long-sustained spasm, still with hardly any movement. The record shows a powerful innervation of all muscles, of about equal strength and synchronous even in small details of pattern. It is easy to conceive that movement must be arrested in a limb when all antagonist groups are simultaneously and maximally active or when a single muscle, such as the sternocleidomastoid here, by maximal sustained contraction holds the head and neck in an extreme position in relation to the trunk. The posture forced on this patient by simultaneous contraction of a majority of his muscles is shown in a photograph (fig. 8). The next two records (*C* and *D*) of figure 7 are from a patient showing the symptoms both of athetosis and of dystonia. Surface leads were used again. They were placed on the biceps, triceps and flexor and extensor groups of the forearm, all on the right side. Record *C* shows all muscles

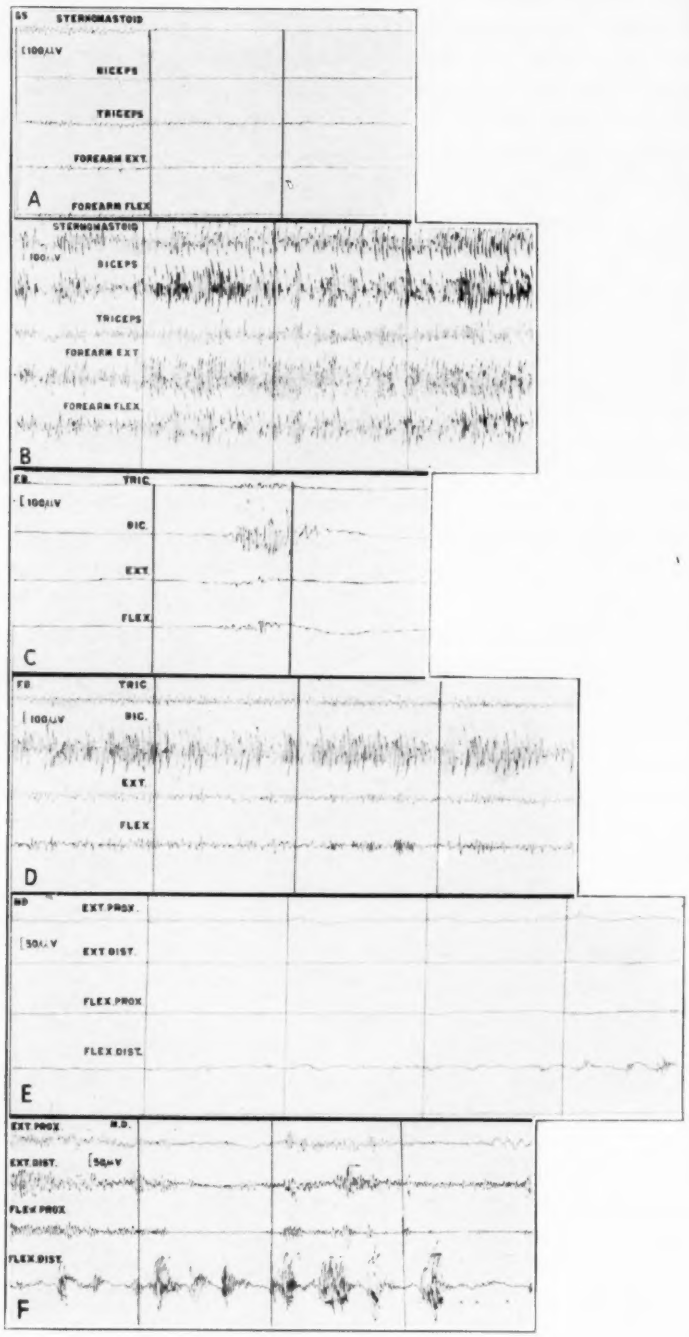

Figure 7

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at rest, interrupted by a short jerk, which is more active in, but not limited to, the muscles of the upper portion of the arm, while in *D* a generalized movement is seen in all four muscles, but with different strengths and patterns. The last two records (*E* and *F*) of figure 7 are from a clearcut case of athetosis. Here two pairs of coaxial needle electrodes were placed in the extensor group and two more in the flexor group of the wrist. In *E* all four motor unit groups are quiet at least most of the time, except for the end of the record, when a movement begins; in *F* is shown one of the bizarre movements of the hand with the asynchronous motor unit activity and, at the same time, the simultaneous irregular antagonist innervation, which has been previously described. In summing up the observations just described, it might be stated that no basic innervation suggestive of "tonic" impulses is seen in athetoid or dystonic muscle during relaxation. The periods of electrical activity coincide with those of active contraction, whether in movement or in simultaneous innervation of antagonists leading to fixation of a limb or of the head and neck in an abnormal posture. Finally, there is no reason to assume the presence of an exaggerated stretch reflex, such as occurs in spasticity (which may, however, coexist).

Tonic Seizures.—It has not been possible to obtain electromyograms of human muscles during the tonic phase of an epileptic seizure. It is reasonable, however, to suppose that observations on animals during induced seizures might be substituted. Merritt and Putnam[12] have successfully employed seizures produced by electrical stimulation of the brain in cats to investigate and standardize anticonvulsant drugs for human use, and the brain potentials recorded during these induced fits in animals correspond closely to those seen in man. A number of obser-

12. Merritt, H. H., and Putnam, T. J.: A New Series of Anticonvulsant Drugs Tested by Experiments on Animals, Arch. Neurol. & Psychiat. **39**:1003 (May) 1938.

EXPLANATION OF FIGURE 7

Involuntary movement in dyskinesis of the dystonia-athetosis group. Time: one second between vertical lines. Calibration marked on each record.

A: "Dystonia." Simultaneous records from surface leads on left sternocleidomastoid, right biceps, right triceps and extensor and flexor groups of the right wrist. Period of almost complete relaxation.

B: Same as in *A*, but during a violent spasm which was almost without movement. Note synchronicity and equal amplitude of action potentials in all leads.

C: Transition between athetosis and dystonia. Surface leads from triceps, biceps, extensor and flexor groups of the wrist on right side. Muscles at rest, interrupted by a quick jerk.

D: Same as in *C*, but during involuntary movement.

E: Athetosis. Motor unit leads of extensors and flexors of the wrist (two each). Muscles at rest.

F: As in *E*, but during athetoid movement.

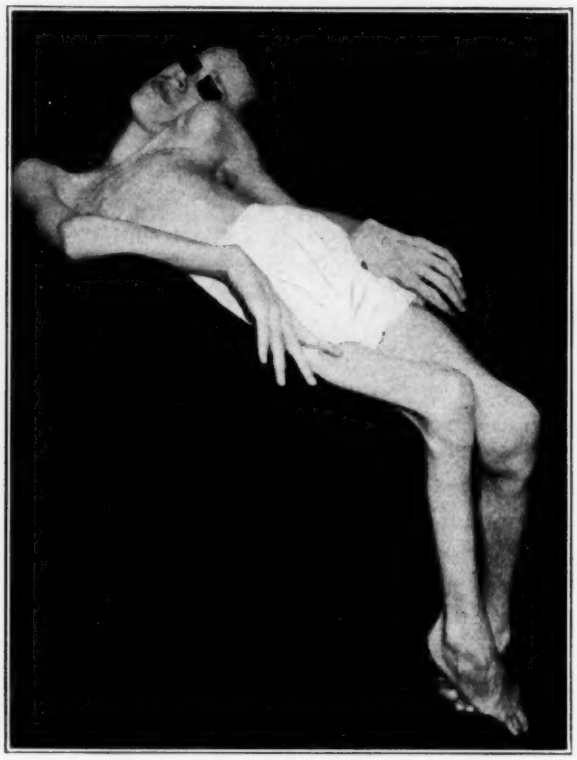

Fig. 8.—Dystonic contraction of muscles without movement, from the same patient as that for whom records are shown in figure 7 *A* and *B*.

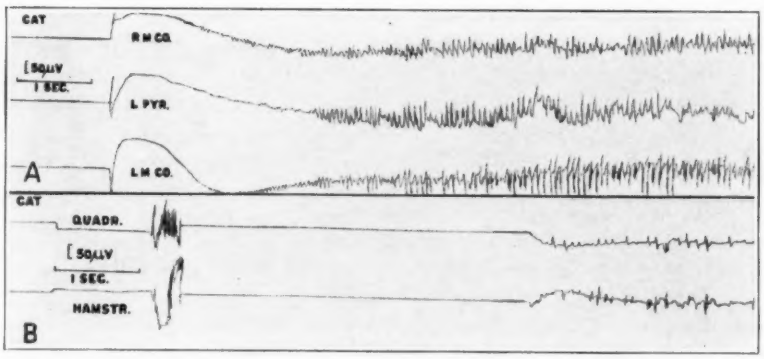

Fig. 9.—Tonic phase of electrically induced seizures in cats, under dial anesthesia. Ink-writing oscillograph. Time: one second marked. Calibration marked on each record.

A: Simultaneous records from right motor cortex, left medullary pyramid and left motor cortex during tonic phase of generalized seizure.

B: Simultaneous records from quadriceps femoris and hamstring musculature during a weak tonic contraction at the beginning of generalized seizure.

vations obtained during current experimental studies on cats under dial anesthesia [13] are presented in figure 9. The first record (*A*) shows the seizure patterns of an induced clinically tonic fit recorded from the exposed right motor cortex, the left medullary pyramid and the left motor cortex. The seizure was induced by faradic stimulation of the right motor cortex and became generalized before the stimulus was shut off. The record shows the patterns of the tonic phase of a grand mal seizure as described by Gibbs, Gibbs and Lennox [14] in all three leads, and it is interesting to note that the impulses are apparently transmitted along the pyramidal tract in the same pattern in which they appear in the cortex. The next record (*B*) shows a short tonic phase of muscle activity in another cat under otherwise identical conditions recorded from the quadriceps femoris and the hamstring group by surface leads. This is only a short, and not extremely powerful, "tonic" extension of the hindleg on the side opposite the stimulated cortex. It should be noted that activity in the two antagonist muscles is synchronous. This is seen more easily in this record, as the relatively weak contraction is accompanied only by a small number of bursts, which, however, occur simultaneously, as they do in the "tonic" state of the "dystonic" patient.

COMMENT

To Sherrington [5] and his school, to name Liddell,[15] Fulton [16] and Denny-Brown,[17] is owed the explanation of the mechanism for postural innervation and its myotatic, proprioceptive regulation. Concerning tone Sherrington (quoted from Cobb and Wolff [18]) stated:

> In regard to [the striated muscles of the skeletal musculature] the word originally, as with Galen (and even in the Renaissance with Fabricius) denoted active posture. In recent years it has regained something of that original meaning. Certainly the trend of experimental evidence is to show postural tonus to be

13. Pool, J. L., and Hoefer, P. F. A.: Tr. Am. Neurol. A., 1941, to be published.

14. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Cerebral Dysrhythmias of Epilepsy: Measures for Their Control, Arch. Neurol. & Psychiat. **39**:298 (Feb.) 1938.

15. Liddell, E. G. T., and Sherrington, C. S.: Reflexes in Response to Stretch (Myotatic Reflexes), Proc. Roy. Soc., London, s.B **96**:212, 1924; Further Observations on Myotatic Reflexes, ibid. **97**:267, 1925.

16. Fulton, J. F.: Muscular Contraction and the Reflex Control of Movement, Baltimore, Williams & Wilkins Company, 1926; Physiology of the Nervous System, New York, Oxford University Press, 1938.

17. Denny-Brown, D.: The Part Played by Afferent Muscular Nerve-Endings in Postural (Tonic) Reflexes, cited by Cobb and Wolff.[18]

18. Cobb, S., and Wolff, H. G.: Muscle Tonus, Arch. Neurol. & Psychiat. **28**:661 (Sept.) 1932.

simply part and parcel of ordinary motility: a manifestation of that ordinary rhythmic neuro-muscular activity by which are executed all our reflex and other acts involving the skeletal musculature. The tonic, i. e., reflex postural form of activity, because mild and static, involves relatively little expensive metabolism, and is little liable to fatigue.

The initial question of this investigation could, therefore, be restated thus: To what extent can the clinical concept of tone be understood in terms of postural innervation? How is postural innervation managed under clinical conditions, and how satisfactory is an analysis of action potentials as compared with information gained by other means?

Tone was one of the main subjects of discussion at the International Neurological Congress held in Berne in 1931. Cobb and Wolff [18] at that time reviewed the situation critically in a report based in part on work presented there. The two outstanding points of this meeting were the physiologic proof of the identity of the mechanisms for postural and for phasic innervation and the anatomic proof, furnished by Wilkinson [19] and Sarah Tower,[20] that the sympathetic innervation of the sarcoplasm, the reputed system for tone, does not exist. There is no "dual system" for kinetic and static innervation as Hunt [21] had postulated it.

Thus the motor cells of the anterior horns with their axons and the muscle fiber groups supplied by the individual axons, the motor units,[22] are the only motor system of the muscle. All centrifugal impulses going to the muscle must travel on the "final common pathway" as motor unit discharges, subject to the "all or none" law.

Electrophysiologic aspects of tone have been studied by a number of earlier investigators.[23] The conventional approach to the problem of tone, however, has been that of mechanical myography. Schaltenbrand,[24] among others, has designed a mechanical myograph for clinical use. An objection to any form of mechanical myography not checked by simultaneous observations on the action potentials, i. e., impulses, is that it is impossible to obtain any information of the condition of the muscle at

19. Wilkinson, H. J.: Experimental Study on the Innervation of Striated Muscle, J. Comp. Neurol. **51**:129, 1930.

20. Tower, S. S.: Further Study of the Sympathetic Innervation to Skeletal Muscle: Anatomical Considerations, J. Comp. Neurol. **53**:177, 1931.

21. Hunt, J. R.: Relation of the Static and Kinetic Systems to Muscle Tone, Arch. Neurol. & Psychiat. **28**:629 (Sept.) 1932.

22. Liddell, E. G. T., and Sherrington, C. S.: Recruitment and Some Other Features of Reflex Inhibition, Proc. Roy. Soc., London, s.B **97**:488, 1925.

23. (*a*) Lewy, F. H.: Die Lehre vom Tonus und der Bewegung, Berlin, Julius Springer, 1923. (*b*) Wacholder, K., and Altenburger, H.: Haben unsere Glieder nur eine Ruhelage? Arch. f. d. ges. Physiol. **215**:627, 1927.

24. Schaltenbrand, G.: Myographische Untersuchungen in der Klinik. Deutsche Ztschr. f. Nervenh. **142**:1, 1937.

rest. Contrary to the current doctrine, the spastic muscle at rest is not in spasm but is relaxed, while in rigidity the muscle shows a constant low degree innervation at rest,[4a] a distinction otherwise difficult to observe. The hypertonicity of spastic muscle is the result of the test (among other causes), while that of "rigid" muscle is due at least partly to internal stimuli from higher centers.

The fact that normal striated muscle at rest shows no action potentials in spite of its slight tension was known to some of the earlier observers, though it has seldom been explicitly stated.[23] Wacholder and Altenburger [23b] and, later, Foerster and Altenburger [25] have shown that slow passive movements in normal persons can be carried out without the production of reflex action potentials in the stretched muscle. They concluded that normally there are several possible positions of rest for a limb. It is of interest to note to what extent in normal subjects adaptation of the muscle tension is possible without nerve regulation. The obvious conclusion, again not explicitly stated before (though Renk and Wöhlisch [26] compared the structure of muscle with that of rubber), is that part of the work is spared because of the intrinsic elastic properties of muscle tissue. Maintenance of the normal standing posture, very nearly effortless in terms of fatigue, as well as of action potentials, is another example of the use of the elastic properties of muscle. It has been shown before [8] that effort and the frequency and height of action potentials are roughly proportionate. As compared with the frequency and height of action potentials during simple voluntary actions, such as lifting a hand or making a fist, minimal exertion goes into standing under normal conditions. The posture is usually maintained by the activity of a small part of the available units, and larger bursts occur apparently only when the distribution of weight is changed by shifting or swaying. The presence of a minimal amount of motor activity in effortless standing is in good correspondence with the observation of Adrian [27] and Matthews [28] that for a constant stimulus, such as stretch, the excitatory process in the receptor, and with it the frequency of impulse discharges in the sensory fiber, decreases in a regular fashion. While adaptation to stretch is slower, for example, than that to touch, it takes place nevertheless, and the reflex motor impulses should be expected to follow a similar, though not necessarily the same, pattern.

25. Foerster, O., and Altenburger, H.: Die Dehnungsreflexe bei Gesunden, Ztschr. f. d. ges. Neurol. u. Psychiat. **147**:169, 1933.

26. Renk, F., and Wöhlisch, E.: Die thermoelastische Anomalie der Skelettmuskulatur und die statistisch-kinetische Theorie der kautschukartigen Elastizität, Arch. f. d. ges. Physiol. **243**:110, 1939.

27. Adrian, E. D.: The Basis of Sensation, New York, W. W. Norton & Company, 1928.

28. Matthews, B. H. C.: The Response of a Single End Organ, J. Physiol. **71**:64, 1931.

At first sight it is not easy to understand why the standing posture of patients with hypotonia should produce action potential patterns not very different from those of normal subjects. A similar question was suggested by the action potential patterns recorded from a patient with spasticity and weakness who was able to stand with support. In every other respect the performances of the muscles in the two disorders differ markedly from each other and from the normal. It has been reported previously [4a] that in spastic patients the "antigravity" muscles may show almost normal strength and a very marked response to stretch, especially the calf muscles. On the whole, however, the spastic muscles are weaker than normal muscles in voluntary effort. It is conceivable that in some instances the hyperreflexia and the weakness compensate each other and that the gross total strength is about normal, especially as it leads to a nearly normal motor performance. It is a little easier to analyze the corresponding mechanism in patients with hypotonia and with apparently abolished myotatic responses, in spite of no obvious loss of afferent impulses in the reflex arc. These patients stand with a visible volitional effort in overcoming their lost reflex function and maintain their balance in a fashion, possibly even by visual regulation, as do patients with ataxia referable to the posterior column. Romberg's phenomenon, usually attributed exclusively to tabetic ataxia rather than to cerebellar dysfunction, is sometimes found in the latter condition.

The response of the spastic muscle to stretch or to heteroceptive stimuli is exaggerated. As a result of brisk contraction of the protagonist, the antagonist becomes involved (by stretch) to a much higher degree than that seen in the normal muscle, so that the resulting movement is stiff and weak, even in cases in which some voluntary control is preserved. The weakness of spastic patients is not caused by lack of power in their muscles. From these observations it seems possible to establish two components of this weakness of effort. There is, first, a diminution in the control of the muscle, which is in proportion to and probably caused directly by the involvement of the corticospinal tracts. As a result, the residual corticospinal fibers at best set off the spinal segmental mechanisms for motor innervation en bloc and with the lack of the characteristic fine adjustment by single motor unit discharges possible under normal conditions.[29] Second, whenever a group of muscles or a single muscle has been activated, the antagonists become involved also by the exaggerated stretch reflex after a brief period of delay. The power available for the planned action is what is left after subtraction of the activity of the antagonists from that of the protagonists.

29. Hoefer, P. F. A.: Physiology of Motor Innervation in the Dyskinesias, A. Research Nerv. & Ment. Dis., Proc. (1940), to be published.

In rigidity the basic simultaneous innervation of antagonists, in addition to a similarly exaggerated stretch reflex, may cause a similar weakness of effort, even when the voluntary control mechanism is intact, as it often seems to be.

The muscle in hypotonia resulting from cerebellar deficit, though it is endowed with good power and though there is no reason to assume that its primary proprioceptive mechanism is disturbed, shows, at least in many instances, no response whatever, even to brisk stretch. The clinical side of this behavior is, of course, hyporeflexia or areflexia. The "pendulous" knee jerk not infrequently seen in cases of cerebellar disorder is most likely not an increased reflex but rather the result of loss of "braking" power caused by flaccidity of the antagonists.[30] While in the present observations normal reflexes have never been found to spread to other levels, simultaneous innervation of the antagonist is not infrequently observed (fig. *2E*). This has also been reported by Altenburger,[31] who has shown that this phenomenon is not an artefact, as it never occurs in cases in which the motor nerve supply to the antagonist has been abolished. Sherrington [5b] (page 285) stated that "concurrent contraction of both antagonists [as seen with the mechanical myograph] scarcely ever results under normal circumstances from simple reflex stimulation of any single point or any single nerve." He has, however, seen "double reciprocal innervation" under special conditions, and it is reasonable to assume that a "subliminal" impulse in the antagonist may be detected before actual mechanical contraction of a measurable degree occurs.

It has already been stated that there is no reason to assume that the muscle of the spastic patient is more taut at rest than that of the normal subject. Similarly, there is no proof that in cerebellar "hypotonia" the muscle is more slack at rest than is the normal muscle.

No cases of peripheral nerve lesions in man were studied during this investigation. So far as the interruption of either the sensory or the motor part of the reflex arc is concerned, the result could be easily predicted to be reduction or loss of postural tone, and animal experimentation bears this out.[32] A small number of control experiments on cats were carried out in order to determine the influence of deafferenta-

30. Holmes, G.: The Cerebellum in Man, Brain **62**:1, 1939.

31. Altenburger, H.: Elektrodiagnostik (einschliesslich Chronaxie und Actionsströmen), in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1937, vol. 3, pp. 747-1086.

32. Brondgeest, P. Q.: Untersuchungen über den Tonus der willkürlichen Muskeln, Arch. f. Anat., Physiol. u. wissensch. Med. **27**:703, 1860. Meyer, A. W.: Experimentelle Untersuchungen über Muskelkontrakturen nach festellenden Verbänden. (2 Mitteilung. Versuche an Warmblütern), Deutsche Ztschr. f. Chir. **162**:147, 1921.

tion on the contraction of muscles in response to electric stimulation.[33] Ten to fifteen days after unilateral section of all posterior roots for the left hindleg, the animals were reexamined while under light anesthesia, which did not abolish the tendon reflexes on the intact side. Both sciatic nerves were exposed for stimulation with maximal induction break shocks. The contractions of both gastrocnemius muscles were recorded simultaneously with muscle levers on a smoked drum.

The excursions produced by contraction of the deafferented muscles were slightly but consistently higher than those of the muscles with the intact nerve supply. Decontraction occurred consistently faster on the deafferented side. After bilateral section of the sciatic nerve there was no difference in the responses on the two sides to single maximal shocks applied to the nerve distal to the section. This seems to indicate that the extent of the contraction and the speed of relaxation are regulated by sensory, especially proprioceptive, control, which, as there is reason to believe, acts on the antagonist. When the steadying influence of the antagonist is lost the movement becomes looser, or "atonic."

In some instances the muscles on the two sides were subjected to powerful passive stretching. Immediately afterward the electrical stimuli were applied as before. The responses of the muscles with normal nerve supply were not measurably changed, while the deafferented muscles showed a peculiar response. This consisted in a slow, incomplete decontraction, comparable to a partial contracture. With repeated single stimuli this residual contracture became more marked, causing a steplike elevation of the "base line." After tetanization with stimuli of the same strength this phenomenon disappeared. It is conceivable that this disturbance of the normal elastic properties of the muscle fibers is prevented by the intact proprioceptive reflex mechanism on the other side, though by what means is not quite clear. It is, however, a clinical experience that "atonic" muscles can be overstretched.

Bilateral section of the sciatic nerves did not cause lengthening of the muscle on either side. The "base line" stayed unchanged. The peculiar deformity of the muscles of a limb associated with a subacute peripheral nerve lesion which causes the musculature to flatten out (*breites Bein* of Monrad-Krohn) was not noted in any of our acute animal experiments. This indicates that neither lengthening nor flattening of a muscle is the immediate result of the loss of nerve control.

In cases of parkinsonian rigidity, and in 1 case of human decerebrate rigidity, a type of innervation has been found and described elsewhere [34] which is not of the myotatic postural type. True, the stretch reflex is exaggerated and in that respect is much like that seen in cases of spas-

33. Moldaver, J.: Personal communication to the author.

34. Hoefer and Putnam.[4] Oppenheim.[9]

ticity, but there is a basic constant influx of low voltage impulses present at rest in patients who are awake, which is presumably of central origin. It appears to be somehow related to tremor (Jackson's "tremor run together"), though in tremor there are, in my opinion, also segmental mechanisms at work.

In describing the observations on patients with athetosis and dystonia it has been pointed out how the impulses presumably of high central origin manage the muscles and how by simultaneous innervation of antagonists both bizarre squirming and fixed abnormal attitude (and everything in between) are produced. It has been mentioned before that Kinnier Wilson [7] called athetosis an "abrogation of Sherrington's law of reciprocal innervation." This statement, on the surface convincing to the clinician, means probably very little. Sherrington developed this concept for the response to cortical and reflex stimulation and, at least to my knowledge, never meant to have its application extended beyond this realm. It is perfectly justifiable to speculate on the possible validity of such a mechanism as reciprocal innervation in the performance of voluntary actions in man. For clinical use, however, Sherrington's whole concept should be taken into consideration, which includes "double reciprocal innervation" of antagonists, a mechanism capable under well defined physiologic conditions [31] of grading movements by simultaneous activation of antagonists.

No manifestations of abnormally active postural reflexes were found in cases in which complications, such as spasticity, did not occur. Nor was any basic activity found at rest, such as is associated with rigidity. "Tonic" contractions of muscles, without movement, here as well as in epileptic seizures, should be understood to be produced by simultaneous equal activation of antagonist muscles through impulses originating above the spinal level. The apparent change from hypertonia to hypotonia in athetosis and dystonia is one from innervation to relaxation. The apparent hypotonia in Sydenham's chorea is probably due to the fact that the periods of innervation here are much shorter and those of relaxation much longer than those in the other dyskinesias. An additional explanation might be the fact that the muscles of children normally are usually less taut than those of adults.

It has been pointed out before by Hoefer and Putnam,[35] and also by Wilson,[7] that certain, not yet well understood, similarities exist between the mode of innervation of the muscles in the dyskinesias and that in cerebellar dysfunction. The motor unit management is similar in the two disorders, as was shown in a previous report.[29]

The diminution of the postural reflex response in cerebellar dysfunction is not easy to understand. The reflex arc with all its components is

35. Hoefer and Putnam (footnote 4 *c* and *d*).

presumably intact. While in spasticity the overfunction of the segmental mechanism is described (rather than explained) as "release" in the absence of the "inhibitory" functions of the corticospinal tracts, the diminution or absence of reflexes associated with cerebellar deficit might be the reverse. It is interesting in this respect to correlate these considerations with recent work by Adrian and Moruzzi.[36] They found that the patterns of the cortical action potentials of the motor area are transmitted in the pyramidal tracts. These observations were repeated and confirmed in our laboratory.[13] The record from a typical experiment, on a cat under moderately deep dial anesthesia (fig. 10), shows simultaneous tracings from both motor areas and from the left medullary pyramid. All records were taken with flat surface electrodes. Synchronous bursts (the synchronicity was probably due to the slow recording speed) are seen to occur every five to eight seconds in the pyramid and the motor cortex on the left side, while the right cortex is out of phase with the left side. No impulses, however, were found in the sciatic

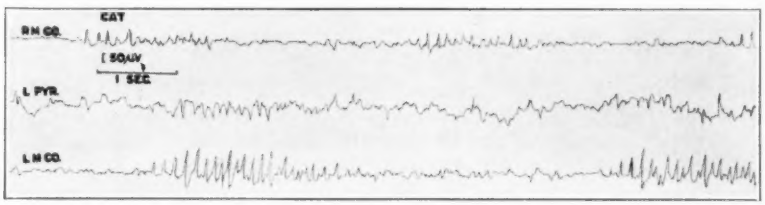

Fig. 10.—Simultaneous records of spontaneous electrical activity of the two motor cortices and the left pyramidal tract (uncrossed, in the medulla) of a cat, under dial anesthesia. Ink-writing oscillograph. Time: one second, marked on record. Calibration marked on record.

Records from above downward are from the right motor cortex, the left pyramid and the left motor cortex.

Note synchronicity of discharges from the left motor cortex and the pyramid, while the right cortex is out of phase.

nerve or in muscles supplied by it, unless during direct cortical stimulation or during epileptic fits. Impulses from cerebral and cerebellar structures might thus keep up a minimal control of the spinal structures at rest, as Adrian and Moruzzi concluded, and it is conceivable, for instance, that by chemical after-effects of impulses the responsiveness of the reflex arc might be modified in various ways.

SUMMARY

An attempt has been made to determine by analysis of action potentials to what extent the clinical concept of normal and abnormal

36. Adrian, E. D., and Moruzzi, G.: Impulses in the Pyramidal Tract, J. Physiol. **97**:153, 1939.

tone of skeletal muscle is covered by that of postural myotatic reflex regulation.

It was shown that normal muscle at rest, in spite of being under a constant slight tension, receives no nerve impulses.

Normally slow changes of posture do not produce nervous regulation of tension of the antagonist, while more brisk changes in posture lead gradually to stretch responses blending into tendon jerks.

Normal, effortless standing requires little nervous regulation, as compared with the work done, and it is concluded that work is spared by utilization of intrinsic elastic properties.

In cases of spasticity no impulses are to be recorded from the muscles at rest. Spasticity is an exaggeration of the normal stretch reflex. The response may be produced by proprioceptive as well as by heteroceptive stimuli.

Rigidity differs from spasticity in that a basic continuous influx of impulses is found at rest, while, in addition, the stretch reflex is exaggerated in a manner very similar to that associated with spasticity. In rigidity a component of "tonic" activity is found which is not understandable in terms of postural segmental regulation.

In cases of cerebellar deficit, in spite of an intact segmental reflex arc, the postural myotatic regulation is decreased or absent. To explain this a concept beyond that of a postural mechanism is required.

No segmental "tonic" mechanism is found in uncomplicated cases of athetosis and dystonia. "Tonic" states are here produced by simultaneous innervation of antagonists.

A similar mechanism is shown to be the cause of the "tonic" phase of epileptic seizures.

A number of physiologic theories are discussed in an attempt to elucidate some of these phenomena.

DISCUSSION

DR. HAROLD G. WOLFF, New York: It is an honor to open the discussion on Dr. Hoefer's paper. The experimental assumptions are sound; the problem is clearly defined; the inferences are justified, and the data are excellently presented. Several facts have been brought into focus by this presentation. First, normal muscle during so-called rest has no action potentials unless the muscle is vigorously and passively moved. Next, even in standing the normal leg muscles show relatively few action potentials because of the highly efficient way in which one muscle unit can take over function after another gives up. Thus, very few units are operating at any one time. Third, the so-called spastic muscle is one which has periods of complete inactivity, similar to that which the normal muscle has, except that the circumstances of that inactivity are more limited than they are for the normal muscle. Thus, even the slightest movement brings forth a shower of action potentials. In contrast, the rigid muscle, for example that of paralysis agitans, gives more or less constant bombardment of action potentials. The muscle of patients with disease of the cerebellum, again, is like the normal muscle;

that is, it has no action potentials during so-called periods of rest. Indeed, the muscle in this condition requires a great deal more passive movement than usual to produce action potentials.

All of these data on muscle and its action potentials are important. What have they to do with "tone"? I find that Dr. Hoefer's data on action potentials are so sufficient, so descriptive and so important to an understanding of the physiology of skeletal muscle activity that they stand alone. For example, to the characteristics of hyperreflexia, the increased response to passive stretch, the lengthening and shortening reaction, the clonus and the extensor plantar response of spastic muscle has now been added the fact that relatively little movement is necessary to bring out a bombardment of action potentials. During certain periods of so-called physiologic rest there may be no potentials at all, in contrast to the state of the rigid muscle of parkinsonism. In short, why not add to what is already known about muscle this additional information on the action potentials? As a matter of fact, the concept of "tonus" may be confusing; for example, Dr. Hoefer stated that "hypertonic muscle" includes both the spastic muscle associated with corticospinal disease and the rigid muscle associated with paralysis agitans. Yet these muscles present entirely different pictures with respect to their action potentials. I fail to see how this concept of "tonus" adds anything to the physiologic understanding of mechanism.

Dr. Abraham M. Rabiner, New York: I should like to ask Dr. Hoefer how he distinguishes between "tonus" and action potentials. For example, when he states that action potentials are absent in the muscles of a normal person who is standing and in the spastic limb of a patient who is lying in bed, does he take into account the production of fatigue in one who is standing and does he eliminate the influence of gravity in producing increased tonus in the spastic limb?

Dr. Paul F. A. Hoefer, New York: I fully agree with Dr. Wolff that "tonus" is an unnecessary word. I am glad that he raised this point, for I am afraid that this term, which is so useful to clinicians and is employed so much, will still be with us for a while. I have tried whenever I have used the term "tone" to put it in quotes.

As for Dr. Rabiner's question, the influence of gravity is sufficient in many instances to set off the mechanism of hyperreflexia.

DIAGNOSIS AND MANAGEMENT OF SUBARACHNOID HEMORRHAGE

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While the subject of subarachnoid hemorrhage has received some consideration from older writers,[1] it is the work of Symonds [2] that has stimulated interest in it in recent times. Generally, the condition is treated under the heading of "spontaneous subarachnoid hemorrhage" and is defined as bleeding into the subarachnoid space due to causes other than trauma. Strauss and his co-workers [3] defined it as massive extravasation of blood into the subarachnoid space caused by spontaneous rupture of the blood vessels. I agree with Smith [4] that the term "spontaneous" is both misleading and meaningless and should be discarded.

Subarachnoid hemorrhage is a symptom, and not a disease entity. It is due to the presence of blood in the subarachnoid space. It results from blood escaping from pial vessels, from ruptured intracranial aneurysm, from massive cerebral hemorrhage that extended to the subarachnoid space, from ventricular hemorrhage and from vascular cerebral neoplasm. It is therefore caused by (1) trauma; (2) arteriosclerotic degeneration of vessel walls; (3) septic or infectious embolism; (4) ruptured intracranial aneurysm; (5) massive cerebral hemorrhage invading the subarachnoid space; (6) intraventricular hemorrhage; (7) blood dyscrasias, and (8) ruptured vascular neoplasm. It has been reported as a complication in metrazol [5] and insulin [6] shock therapy of the psychoses.

Read before the Section on Nervous and Mental Diseases at the Ninety-Second Annual Session of the American Medical Association, Cleveland, June 6, 1941.

1. Bramwell, B.: Clinical and Pathological Memoranda, Edinburgh M. J. **32**:1 (July) 1886. Ehrenberg, L.: Spontaneous Subarachnoid Hemorrhage, Hygiea **74**:849 (Aug.) 1912. Leopold, S.: Spontaneous Subarachnoid Hemorrhage, J. A. M. A. **83**:1362 (Oct. 17) 1914. Ingvar, S.: Sur les hémorragies méningées, Nouv. iconog. de la Salpêtrière **28**:313, 1916.

2. Symonds, C. P.: Spontaneous Subarachnoid Hemorrhage, Quart. J. Med. **18**:93 (Oct.) 1924.

3. Strauss, I.; Globus, J., and Ginsburg, S. W.: Spontaneous Subarachnoid Hemorrhage, Arch. Neurol. & Psychiat. **27**:1080 (May) 1932.

4. Smith, W. A.: Spontaneous Subarachnoid Hemorrhage, South. M. J. **22**: 494 (June) 1930.

5. Roback, H. N., and Miller, C. W.: Subarachnoid and Intracranial Hemorrhage Due to Metrazol, Arch. Neurol. & Psychiat. **44**:627 (Sept.) 1940.

6. Freed, H., and Wofford, C. W.: Subarachnoid Hemorrhage During Shock Therapy for Schizophrenia, Arch. Neurol. & Psychiat. **39**:813 (April) 1938.

Hemorrhage into the subarachnoid space causes general, as well as focal, symptoms. The general symptoms are due to diffuse irritation and compression of the brain and to meningeal irritation. The focal symptoms are due to irritation or disturbed function of certain parts of the nervous system. As the blood escapes into the subarachnoid space, intracranial pressure increases, causing headache, vomiting and dizziness. The headache may at first be localized to the nape of the neck, radiating upward toward the vertex, or the pain may be referred to the regions innervated by the fifth cranial nerve and presumably cause irritation of some or all of its branches. The pain is occasionally referred to either eye. The blood travels from the subarachnoid space along the sheaths of the optic nerves, causing blurring of the margins of the disks, and even papilledema.[7] In the average case the eyegrounds present almost a pathognomonic picture; that is, the center of the disk appears more elevated than the periphery, and the margin is generally clearly outlined and the veins are not very tortuous, though they may be congested. The pressure in the optic sheath may cause obstruction of the central vein of the retina at a point where it leaves the optic nerve and enters the dural sheath,[8] resulting in increased intraocular venous pressure and producing retinal hemorrhages. As the blood invades the sheaths of the other cranial nerves it produces disturbance of their functions. Thus, it may cause pupillary disorders, extraocular palsies, facial pareses, deviation of the tongue, and even of the lower jaw, ringing in the ears, difficulty in swallowing and respiratory and cardiac disturbances. The pupils may present a striking phenomenon—namely, marked variability in size, shape and reflexes from day to day. The pupils may be unequal in size; one or both may be irregular in outline, they may fail to react to light or in accommodation or they may show the paradoxic light reaction. Pressure on one or both of the pyramids may result in hemiparesis or hemiplegia. The abdominal reflexes are generally sluggish; they may even be absent, or occasionally they may be retained. The deep reflexes, especially those of the lower extremities, are usually markedly depressed at first; they may, however, be present, and even overactive. As the blood passes down the spinal subarachnoid space, it causes irritation of the dorsal roots, resulting in pain, particularly in the lower part of the back with radiation to the thighs. Convulsions occasionally occur. All degrees of disturbances of conscious-

7. Doubler, F. H., and Marlow, S. B.: A Case of Hemorrhage into the Optic Nerve Sheaths, Arch. Ophth. **46**:533 (Nov.) 1917. Dawson, D. I.: Spontaneous Subarachnoid Hemorrhage, Wisconsin M. J. **22**:426 (Feb.) 1924. Griffith, J. Q.; Jeffers, W. E., and Fry, W. E.: Papilledema Associated with Subarachnoid Hemorrhage, Arch. Int. Med. **61**:880 (June) 1938.

8. Calhoun, F. P.: Ocular Symptoms in Subarachnoid Hemorrhage, J. A. M. A. **87**:1104 (Oct. 2) 1926.

ness, from transitory confusion to coma, may be encountered. There is marked nuchal rigidity, and the Kernig sign may be present. However, this sign is usually mild and never of the severity encountered in cases of infectious meningitis, apparently because the blood is less irritating to the posterior nerve roots than are the purulent exudates present in infectious meningitis. I have had 3 patients with ruptured intracranial aneurysm who were comatose and flaccid but who showed marked nuchal rigidity after spinal puncture.

The presence of blood in the subarachnoid space acts as a foreign, irritating substance, producing leukocytosis and elevation of the temperature. The number of leukocytes is hardly ever above 14,000, and the polymorphonuclears are usually between 65 and 80 per cent. The leukocytosis may be used as a diagnostic and prognostic sign, for a high degree of leukocytosis, with a count of over 20,000, generally points to a massive cerebral hemorrhage, to a ventricular hemorrhage or to continuation of the bleeding and carries with it an unfavorable prognosis.[9] The temperature ranges from 99 to 101 F., or at the most 102 F., continues at that elevation for about a week and gradually subsides to normal. A higher temperature, such as 104 and 105 F., usually indicates a massive cerebral lesion, with an unfavorable prognosis. The pulse rate is usually slow, 60 or less per minute, or when accelerated because of high temperature, it is still relatively low as compared to the elevated temperature. A persistently rapid pulse is an unfavorable sign. Occasionally one finds albumin in the urine which cannot be accounted for on a renal basis. This has been discussed in the literature under the heading of "massive albuminuria" [10] and is used as a sign in the diagnosis of subarachnoid bleeding. However, this phenomenon has not been present in any of my cases.

The clinical course will depend to a certain extent on the etiologic process causing the subarachnoid hemorrhage. The onset, as a rule, is sudden, usually following some physical exertion or emotional tension. Many patients describe the initial sensation as that of being struck a powerful blow on the back of the head. Others give a history of prodromal symptoms, such as episodic attacks of headache, dizziness and nausea.

The spinal fluid in this condition is pathognomonic of the syndrome. The fluid is uniformly bloody when collected in several test tubes. It varies in intensity of color, depending on the amount of blood which it contains. When permitted to stand for a while, the red blood cells

9. Musser, J. H.: The Leucocytes After Hemorrhage, Am. J. M. Sc. **162**:40 (July) 1921.

10. Widal, F.: Le diagnose de l'hémorragie méningée, Presse méd. **11**:413 (June 3) 1903.

sink to the bottom, and the supernatant fluid is golden yellow or orange, a condition which is referred to as xanthochromia. No coagulation of the blood occurs in the spinal fluid.

Subarachnoid hemorrhage has been encountered in several of the group of cases of so-called sudden death and, therefore, has a medicolegal implication.[11]

The syndrome of subarachnoid hemorrhage has frequently been mistaken for (1) septic meningitis, (2) sinusitis, (3) encephalitis, (4) tumor of the brain, and (5) uremia. The cervical rigidity, the Kernig sign, the pyrexia and the leukocytosis may lead to the diagnosis of septic meningitis. The headache, the vomiting, the photophobia and the elevation of temperature may suggest sinusitis. The drowsiness, the pupillary disorders and the involvement of the cranial nerves may simulate encephalitis. The headache, the changes in the eyegrounds, the convulsions, the vomiting and the unconsciousness may lead to the diagnosis of cerebral tumor. The loss of consciousness, the convulsions and the albuminuria may simulate a uremic condition. I encountered an instance of a hysterical reaction which simulated subarachnoid hemorrhage in a young intern. He was found lying at the foot of the stairs leading from the main ward; his head was markedly retracted and he appeared to be unconscious, but no other focal signs were encountered. A tentative diagnosis of traumatic subarachnoid hemorrhage was made, but the inhalation of strong ammonia aroused him and after discussion of his problem he was able to resume his duties in two days.

Analysis of Cases of One Hundred and Twenty Patients with Subarachnoid Hemorrhage

Cause	Sex		Total Number	Died	Recovered
	Male	Female			
A. Unknown	20	7	27	4	23
B. Secondary to:					
(1) Trauma	7	2	9	1	8
(2) Arteriosclerosis	14	16	30	3	27
(3) Infectious diseases	7	9	16	9	7
(4) Intracranial aneurysm	10	15	25	12	13
(5) Massive cerebral hemorrhage	1	1	2	2	0
(6) Intraventricular hemorrhage	2	1	3	3	0
(7) Blood dyscrasias	3	1	4	4	0
(8) Cerebral vascular neoplasm	1	3	4	3	1
	65	55	120	41	79

A report is made on a series of 120 hospital patients observed personally during a period of eighteen years (table). I have divided them into two main groups: (1) those with subarachnoid hemorrhage due to unknown or as yet undetermined causes, and (2) those with

11. Ayer, W. D.: So-Called Spontaneous Subarachnoid Hemorrhage: Résumé with Its Medicolegal Consideration, Am. J. Surg. **26**:143 (Oct.) 1934.

secondary subarachnoid hemorrhage, in which the bleeding followed trauma, arteriosclerotic degeneration of a vessel wall, septic or infectious embolism, septic degeneration of the vessel walls, ruptured intracranial aneurysm, massive cerebral hemorrhage invading the subarachnoid space, intracranial hemorrhage, blood dyscrasia or ruptured vessels in a vascular neoplasm.

With the foregoing consideration of the general features of the subject, the following cases are reported.

SUBARACHNOID HEMORRHAGE DUE TO UNKNOWN OR UNDETERMINED CAUSES

In this group are included those cases in which the symptoms were mild and the patients generally were relatively young. There were no signs of a focal lesion. It is likely that in many instances the hemorrhage may have been due to unrecognized miliary aneurysm. Furthermore, it is quite possible that in some it may have resulted from rupture of a vessel wall due to a focal degenerative arteriosclerotic lesion. The theories that the condition may be due to diapedesis [12] or to a functional vasomotor disturbance [13] analogous to what is supposed to occur in Raynaud's disease lack confirmation. Twenty-seven cases are listed in this group (table). The following cases are illustrative.

CASE 1.—J. G., a married man aged 25, was admitted to the Beth-El Hospital on Dec. 27, 1931, complaining of drowsiness and of headache for two days. On the night preceding the illness he indulged in excessive sexual relations. At 12 noon he suddenly experienced a severe headache and became delirious and then drowsy, remaining so until his admission to the hospital. When examined, his pupils were contracted, and the corneal and pharyngeal reflexes were absent. There was rigidity of the neck, with practically no Kernig sign. The eyegrounds showed excessive retinal engorgement with slight blurring of the margins of the disks. The knee jerk and ankle jerk were graded 1 plus on the right and were absent on the left. The blood count showed 5,000,000 red cells, 102 per cent hemoglobin and 10,800 white cells, with 87 per cent polymorphonuclears. The Wassermann reaction of the blood was negative. The chemical constituents of the blood were normal. The spinal fluid was bloody when collected in three test tubes and was under moderately increased pressure. For a week the patient was drowsy and the meningeal signs were prominent, the nuchal rigidity persisting and a Kernig sign developing on the third day. The pupils varied daily in their reaction and in their size and shape. The left pupil at times showed a paradoxic reaction. The right knee jerk was occasionally elicited, while the left was absent. On January 13 weakness of both external rectus muscles developed. The blurring and hyperemia of the eyegrounds increased. On January 15 he showed distinct improvement. His temperature on admission was 100.2 F., his pulse rate 60 and his respiratory

12. Neylan, K.: Ueber spontanen diffuse Meningenblutungen, Deutsche Ztschr. f. Nervenh. **78**:78, 1923.

13. Goldflam, S.: Beiträge zur Aetiologie und Symptomatologie der spontanen subarachnoidalen Blutungen, Deutsche Ztschr. f. Nervenh. **76**:158, 1923.

rate 20. The results of several examinations of the urine were normal in every respect. The temperature remained between 100 and 101 F. for about two weeks and then became normal. His condition gradually improved, and he was discharged on January 20, free from symptoms.

CASE 2.—H. G., a single man aged 23, was admiitted to the Coney Island Hospital on Aug. 4, 1932 and was discharged on August 26. On the day prior to admission he had complained of headache and was somewhat drowsy. Examination revealed he was semistuporous. He was cooperative when aroused. He complained of headache, constantly passing his hand across his forehead. His pupils were irregular in outline and reacted sluggishly to light. The eyegrounds showed definite vascular engorgement and blurring of the margins of the nasal halves of the disks. There were suggestive weakness of the left side of the face and slight deviation of the tongue to the left. The abdominal reflexes were exhaustible on the right and active on the left. The deep reflexes were absent. There were marked rigidity of the neck and a moderate Kernig reaction. The chemical constituents of the blood were normal. The blood count showed 9,500 white cells, with 72 per cent polymorphonuclears. The pulse rate was 60. The temperature was 101 F. for five days and finally became normal. His condition gradually improved, and he was discharged from the hospital.

Of the 27 patients comprising this group, only 1 died in the hospital. In the entire series of 120 he was the only one who presented incontrovertible evidence, clinical and serologic, of neurosyphilis. Necropsy [14] showed extensive hemorrhage at the base and the vertex of the brain, and microscopic examination revealed diffuse syphilitic meningoencephalitis. Three of the remaining patients died within a month after they had left the hospital. One patient had five attacks of subarachnoid bleeding within ten years, 1 of them occurring during pregnancy.

SECONDARY SUBARACHNOID HEMORRHAGE

In contrast to the cases just reported, the patients in the following cases suffered from definite pathologic conditions which might account for the subarachnoid bleeding.

Traumatic Subarachnoid Hemorrhage.—Trauma to the head may cause injury to the small pial vessels, resulting in subarachnoid hemorrhage and manifested by signs of meningeal irritation, as well as compression of the brain. The blow causing the hemorrhage may not be a heavy one. The term traumatic subarachnoid hemorrhage should be limited to that form which one may be reasonably certain is due not to severe damage to the brain but merely to injury to fine meningeal vessels, resulting in the escape of blood into the subarachnoid space and producing the classic symptoms of subarachnoid hemorrhage. Nine cases of this type comprised this group. In all but 1 the patients recovered—a 4½ year old microcephalic boy who had been having convulsions since

14. Sands, I. J.: Subarachnoid Hemorrhage as a Clinical Complication of Neurosyphilis, Arch. Neurol. & Psychiat. **24**:85 (July) 1930.

the age of 6 months. He was subjected to pneumoencephalographic examination. After this procedure a high temperature, nuchal rigidity and coma developed. He died forty-eight hours later. Necropsy revealed extensive hemorrhage over the vertex and base of the brain (fig. 1 *A* and *B*) and thrombi in the venous sinuses. It was the opinion expressed by the physicians who had examined the boy that the subarachnoid bleeding was secondary to the pneumoencephalographic procedure and was of "traumatic" nature. The following cases are illustrative.

CASE 1.—M. K., a white man aged 42, a baker, was married and had 6 children. On Oct. 30, 1926 he was struck on the point of his chin. He fell backward, striking the occipital region. He was stunned for a few moments and had to be helped to his feet. He immediately complained of severe occipital headache, which radiated to the front of the head. He was taken home in a taxicab. He complained of headache, dizziness and nausea. On the following morning he was unable to get out of bed to go to work because of weakness, dizziness and headache. He remained in bed for four days, being unable to get up because of these distressing symptoms. He was sent to the Beth-El Hospital. Examination revealed slight cervical rigidity, widely dilated pupils and hyperemia of the disks. His reflexes, sensation and coordination were intact; no pathologic reflexes were elicited. The pulse rate was 52, the temperature 98 F. and the respiratory rate 18. The blood count was 8,440 white cells, with 60 per cent polymorphonuclears. The chemical constituents of the blood were normal. The Wassermann reaction of the blood was negative. The spinal fluid was golden yellow and under increased pressure; the Wassermann reaction was negative. A roentgenogram showed no evidence of fracture of the skull; venous channels were somewhat increased in prominence. The blood pressure was 130 systolic and 85 diastolic. The patient complained of dizziness and of headache, especially on change of position. His pulse remained slow for four days, varying from 50 to 60 a minute. He received daily lumbar punctures. The color in the spinal fluid gradually faded, until it disappeared on the ninth day. The patient was discharged on September 14.

CASE 2.—H. G., a 12 year old boy, was admitted to the Coney Island Hospital on Jan. 25, 1939. While running home from school, he slipped on the ice and fell, striking the back of his head. A hematoma developed. He vomited but continued on his way home. Within a few minutes after reaching his home he became drowsy and very restless, and the temperature rose to 100 F. His pulse was 60 and his respiratory rate 18 per minute. Examination showed moderate nuchal rigidity and a very mild Kernig sign. The deep reflexes were depressed. There were no pathologic reflexes. The pupils were equal and reacted rather sluggishly. The eyegrounds showed marked hyperemia of the nerve heads, particularly at the center, but the outlines of the disks were distinct. The blood count showed leukocytosis, with a white cell count of 11,500, 72 per cent of which were polymorphonuclears. The urine showed a faint trace of albumin. A roentgenogram of the skull disclosed a linear fracture of the left occipital region adjacent to the parieto-occipital suture line. The fluid from lumbar puncture was collected in three test tubes and was uniformly bloody. On the following two days the temperature rose to 101 F., but the patient appeared to be fairly comfortable. At the end of a week the temperature and pulse were normal. After a residence of three weeks the patient was discharged free from symptoms.

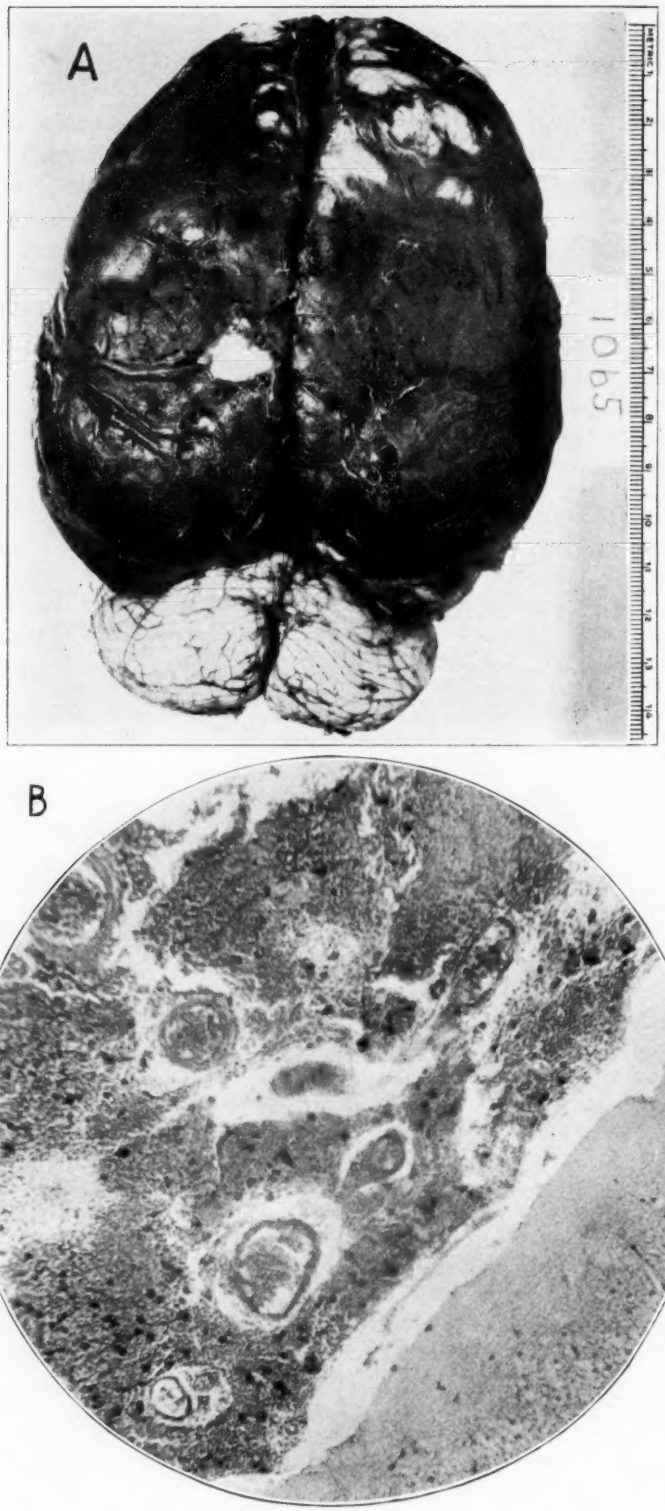

Fig. 1.—*A*, subarachnoid hemorrhage following encephalography. *B*, subarachnoid space filled with blood and macrophages.

Arteriosclerotic Subarachnoid Hemorrhage.—Arteriosclerotic degeneration of the vessel wall may produce subarachnoid leakage, either by formation of an aneurysm which has ruptured or by rupture of degenerated small capillaries or possibly by general oozing. Usually the patient will show evidences of arteriosclerosis in the other organs of the body. Retinal arteriosclerosis is usually present. Many patients may have had hypertension for years. Others may show some cardiac or renal involvement. Of the 30 patients comprising this group, 3 died while under treatment in the hospital. In this particular group abnormal neurologic signs are frequently encountered, and the cause of the hemorrhage is apt to be regarded as aneurysmal. However, I have dissected the arterial system in a few such patients and have failed to detect any macroscopic aneurysm. Occasionally the condition may even be considered as massive cerebral hemorrhage. The following cases are illustrative.

CASE 1.—E. K., a 46 year old woman, a psychiatric social worker, was admitted to the Jewish Hospital on Feb. 27, 1937 and died on March 14. Eight years ago she had urticaria; at that time a growth on the breast was removed. Her menses had been regular until one year ago; since then they had been somewhat irregular. On the day of admission the patient suddenly had pain on the top of the head, which increased in severity. She became nauseated and induced vomiting. The headache persisted, and stiffness of the neck ensued. On admission the patient was very drowsy and complained of headache. The pupils were equal, and the left did not react well. The eyegrounds were relatively normal. The left angle of the mouth drooped slightly. There was marked rigidity of the neck, and a mild Kernig sign was elicited. All the deep reflexes were depressed. An equivocal Babinski sign was elicited on the left. The spinal fluid was bloody and under a pressure of 120 mm. The patient continued to be drowsy; on March 7 there were deviation of the tongue to the left and left hemiplegia but no pathologic reflexes. On admission her temperature was 100 F. and remained so for four days, when it rose to 102 F. and persisted at that elevation throughout the rest of her illness. Her blood pressure was 160 systolic and 105 diastolic. Her pulse varied between 80 and 120. The urine showed a 1 plus reaction for albumin. The blood count showed 15,650 white cells, with 87 per cent polymorphonuclears, and 4,000,000 red cells, with 30 per cent hemoglobin. The Wassermann reaction of the spinal fluid and blood were negative. Several consultants examined the patient, and finally one diagnosed her condition as that of meningeal and intracerebral apoplexy due to hypertension and advised operation. A right temporal decompression was done. The cortex was incised, but no massive cerebral hemorrhage was found. After the operation her temperature rose to 104 F., and she died.

Autopsy.—The brain weighed 1,190 Gm. There was a slight cerebellar pressure cone. Over the right parietal and both occipital lobes (fig. 2 *A*) there was a massive extravasation of blood, which filled all the sulci. A ragged opening, 1.5 by 0.5 cm., was present at the junction of the rolandic and the sylvian fissure on the right side. The convolutions were flattened, and the sulci were narrowed. The walls of the large vessels at the base of the brain showed yellow, opaque patches. The left posterior cerebral artery was narrowed. The right posterior communicating artery

was threadlike. Careful examination of all the vessels failed to disclose any aneurysmal formation. Sections of the brain disclosed a normal ventricular system. A definite hemorrhagic tract (fig. 2*B*) indicated the course of the needle at

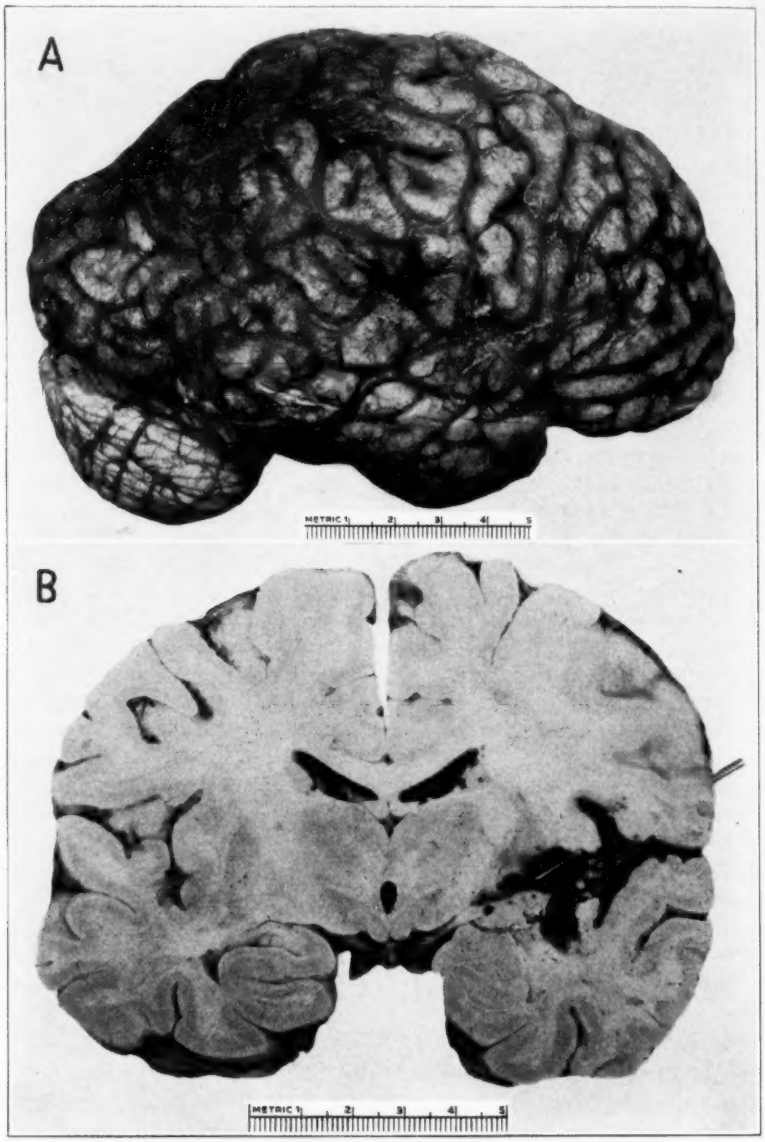

Fig. 2.—*A*, pia-arachnoid hemorrhage. Note incision made at operation. *B*, section showing tracts made at operation.

operation. Microscopically, numerous red blood cells were seen infiltrating the pia and the arachnoid. Many mononuclear cells were present. The large vessels, as well as smaller capillaries, showed evidence of atheromatous changes, with definite

thickening of the walls, loss of muscle fibers, increase in connective tissue and splitting and reduplication of the elastic layers. In addition, the autopsy disclosed healed mitral stenosis; a thrombus in the left pulmonary artery, with infarction of the lung; chronic cholecystitis and cholelithiasis, and fatty degeneration of the liver.

CASE 2.—T. L., a white woman, the mother of 3 children, was admitted to the Jewish Hospital of Brooklyn on March 4, 1941, complaining of severe headache. On the night of March 2 she was in the bathroom, straining at stool, when she suddenly experienced a sharp pain in the back of her head. She lost consciousness for a few minutes, and when she awoke she walked to her bed. On the following day she had a dull headache. In the afternoon she suddenly lost consciousness and had a mild convulsion. When she regained consciousness, she complained of severe headache. The neurologic examination disclosed marked rigidity of the neck and a bilateral Kernig sign. There was mild weakness of the left external rectus muscle. The pupils were equal and slightly irregular in outline, and the eyegrounds showed definite retinal arteriosclerosis, with hyperemia of the nerve heads, particularly in the center. All the deep reflexes were depressed. There was loss of the left plantar reflex, and the left abdominal reflexes were very sluggish. Spinal puncture yielded a bloody spinal fluid, which was obtained under pressure of 350 mm. of water. Chemical examination of the blood showed 95 mg. of sugar and 10.7 mg. of urea nitrogen per hundred cubic centimeters. The sedimentation rate was 40 mm. an hour. The blood count showed 4,250,000 red cells, 65 per cent hemoglobin and 10,250 white cells, with 68 per cent polymorphonuclears. Her temperature on admission was 99 F. and her pulse rate 60 per minute. The temperature rose to 102 F. and remained so for three days and then gradually declined to normal. She remained in the hospital for four weeks and was discharged to her home, where she resumed her household duties. On April 16 she had a bad dream which aroused her from sleep, and she experienced an excruciating pain in the occipital region, radiating to the right side of the head and to the frontal region. The headache persisted until her admission to the hospital on April 18, 1941. On examination she presented marked nuchal rigidity with a mild Kernig sign. The pupils were equal and reacted well. The eyegrounds showed hyperemia of the nerve heads. There were a suggestion of slight hyperreflexia and an equivocal Oppenheim reflex on the left. The urine contained a rare pus cell. Her blood count showed 4,900,000 red cells, 81 per cent hemoglobin and 17,200 white cells, with 78 per cent polymorphonuclears. The sedimentation rate was 100 mm. an hour. Chemical analysis of the blood showed 100 mg. of sugar and 11 mg. of urea nitrogen per hundred cubic centimeters. The initial pressure of the spinal fluid was 330 mm. The fluid was bloody and contained 16,300 red cells per cubic millimeter. The Wassermann reactions of the blood and spinal fluid were negative. The patient's illness ran an uneventful course, and she was discharged on May 11, 1941.

Subarachnoid Hemorrhage Complicating Infectious Diseases.—Bacteria and their toxins may cause inflammatory and degenerative processes in the small vessels, which may result in their rupture. Of the 16 patients comprising this group, 7 recovered and 9 died. Three patients presented simultaneous signs of appendicitis and of subarachnoid hemorrhage, each having an appendectomy and each recovering from both conditions. It was felt that the same infectious agent was responsible for the appendicitis and for the changes in the blood capillaries producing

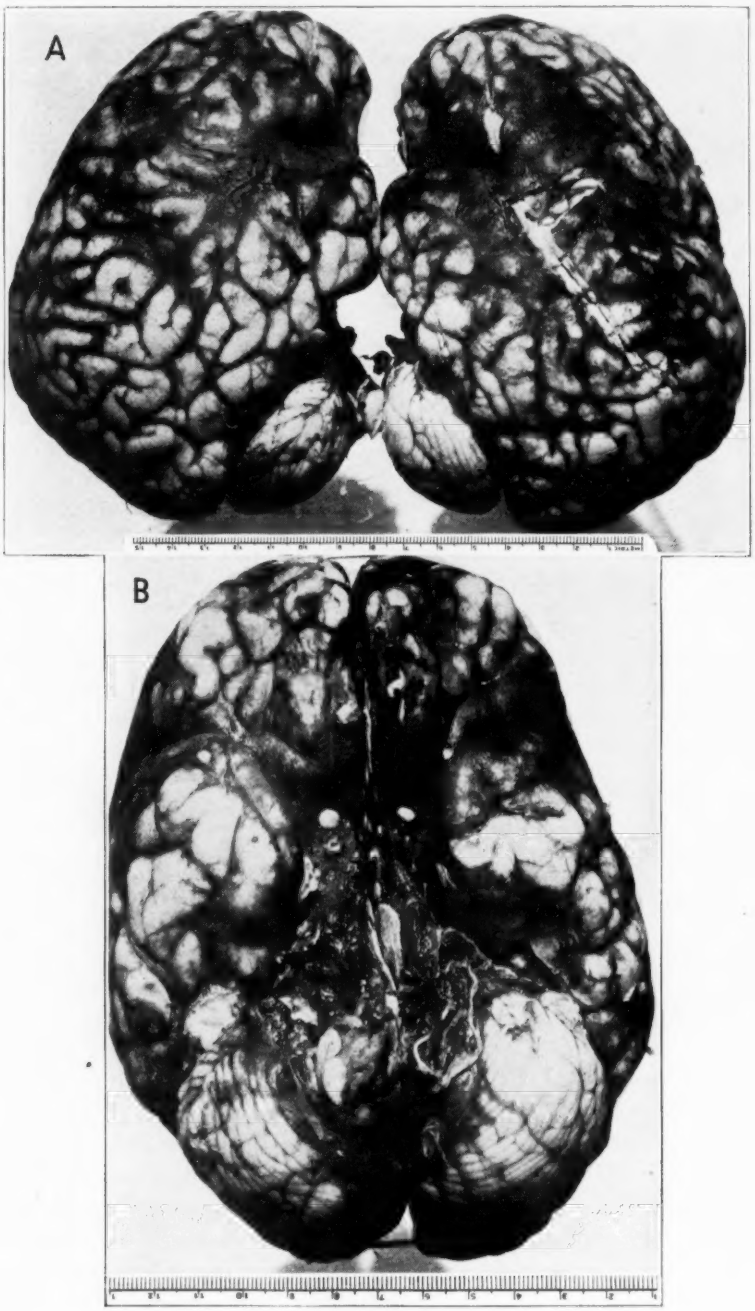

Fig. 3.—*A* and *B*, subarachnoid hemorrhage complicating encephalitis.

the subarachnoid bleeding. Two patients had septic sore throat and subarachnoid hemorrhage, and each recovered. In another patient signs of subarachnoid bleeding developed a few weeks after his recovery from meningococcic meningitis. It was felt that the meningitis had caused changes in the blood vessels which were the basis for the subarachnoid bleeding. In 2 patients subarachnoid bleeding complicated whooping cough. One recovered and the other died. Necropsy showed extensive hemorrhage both over the surface and at the base of the brain and marked destruction of the frontal lobes and the corpus striatum and thalamus, resulting from confluent pericapillary hemorrhages. One

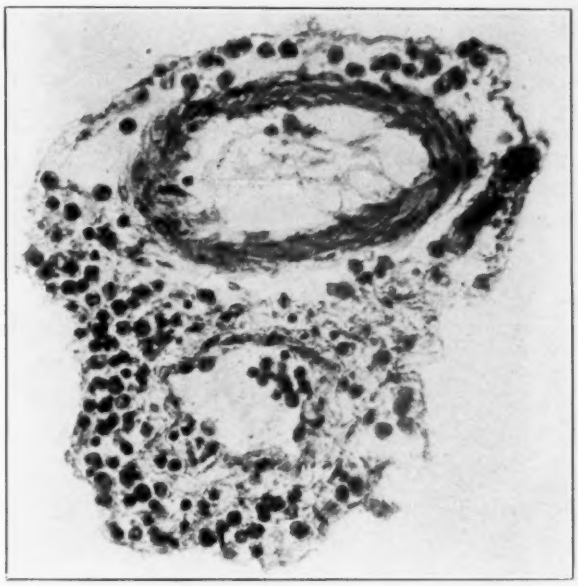

Fig. 4.—Inflammatory reaction in a pial arteriole in a case of subacute bacterial endocarditis.

patient had encephalitis (fig. 3) and ten days later presented a syndrome of subarachnoid hemorrhage; death occurred two days later, after a convulsion, and necropsy revealed extensive subarachnoid bleeding and diffuse encephalitis. In another patient evidence of subarachnoid hemorrhage was the first manifestation of subacute bacterial endocarditis, proved clinically as well as at autopsy (fig. 4). Another patient had streptococcemia, streptococcic pneumonia, meningitis and evidence of subarachnoid hemorrhage; another had acute nephritis superimposed on chronic glomerular nephritis, with convulsions and the syndrome of subarachnoid hemorrhage; in both instances the diagnoses were confirmed, at necropsy. A primipara was in labor for three days, suddenly went into shock, became drowsy and presented a syndrome of subarachnoid

bleeding. She died within eight hours of onset of the symptoms, and necropsy showed extensive hemorrhages covering the cerebellum, medulla and pons, streptococcic pneumonia and hemorrhages into the stomach and adrenal glands. Another patient had measles and four days later showed signs of meningeal irritation and blood in the spinal fluid and died within two days; at necropsy purulent mastoiditis, thrombosis of the superior longitudinal, left lateral and left zygomatic sinuses and extensive subarachnoid hemorrhages were observed. A 10 year old boy who had congenital heart disease and had presented the tetralogy of Fallot for many years suddenly complained of headache and had a

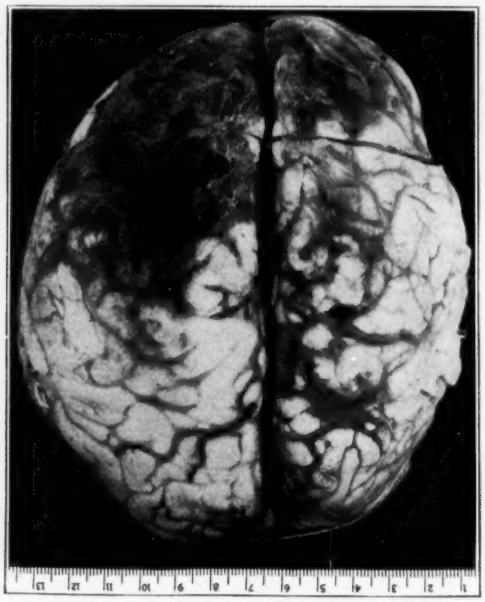

Fig. 5.—Pia-arachnoid hemorrhage.

temperature of 102 F. Two days later evidence of marked meningeal irritation developed, and examination of the spinal fluid disclosed pus mixed with blood. He died three days later, and at necropsy two abscesses of the brain were noted, one of which had broken into the meninges and apparently eroded a capillary, producing subarachnoid bleeding.

The following cases are illustrative.

Case 1.—H. C., a girl aged 2 years 4 months, was admitted to the Jewish Hospital on April 9, 1926 and died on the same day. The family history was noncontributory. She was born at full term, of a normal delivery, and developed normally. On March 29, measles developed. Five days after onset of the illness she had a temperature of 104 F. Her respirations became markedly accelerated and

labored. She coughed frequently. On April 8 she became drowsy and vomited. On admission she was stuporous. The pupils were moderately dilated but reacted promptly. The vessels of the disk were engorged. There was no cervical rigidity or Kernig sign. The Babinski sign was present bilaterally. The heart and lungs were apparently normal. Spinal puncture disclosed a bloody fluid which was under increased pressure. No organisms were obtained on smear or in culture. The blood count showed 3,200,000 red cells, 72 per cent hemoglobin and 15,600 white cells, with 63 per cent polymorphonuclears. The ear drums were described as normal. On the day of admission the child suddenly became cyanotic and stopped breathing.

Autopsy.—The brain weighed 1,000 Gm. The dura was clear and glistening. On removal of the brain a large hemorrhage covering the upper surface of both frontal lobes (fig. 5) was observed. The inferior surfaces of the left frontal and left temporal lobes were also covered by the hemorrhage. The left lateral and zygomatic sinuses were filled with an organized thrombus, which extended into the superior longitudinal sinus and was present throughout its entire length. When the mastoids were opened yellow pus exuded. Cultures of material revealed a nonhemolytic streptococcus. There were also pulmonary edema and congestion and thrombosis of the pulmonary veins, fatty degeneration of the liver, congestion and fibrosis of the spleen and tubular degeneration of the kidneys. Microscopically, the pia showed considerable free blood in its meshes. There were numerous macrophages containing blood pigment and debris. The fibroblastic elements were increased. The wall of the lateral sinus was considerably thickened, and the thrombus within the sinus was organized. The nerve cells showed no particular changes. The neuroglia was moderately increased. There were no signs of an inflammatory reaction.

CASE 2.—M. B., a married housewife aged 38, was admitted to the Jewish Hospital on Nov. 5, 1926 and died November 9. She was a primipara at term. The pains started six hours before admission, and the membranes ruptured five hours later. She was having pains every three minutes. The pains then stopped. On the morning of November 8 the patient appeared to be in shock and became somewhat drowsy but was conscious. The pulse was small and regular, and the rate was 140 per minute. She was thirsty. The blood pressure was 160 systolic and 100 diastolic. A bag was inserted and was later expelled, followed by fresh blood clots and considerable oozing. It was decided to perform a cesarean section. While preparations for the operation were being made, at 5:30 p. m. on November 9, the patient's eyelids suddenly started to twitch, and the respirations became slow and irregular, with periods of apnea. There was blurring of both eyegrounds, with moderate edema of the disks. The cranial nerves were apparently not involved. There was flaccidity of all extremities. The deep reflexes were present but diminished. No pathologic reflexes were elicited. No cervical rigidity or Kernig sign was present. The pulse was rapid (130 plus), and the respirations were markedly slow. The patient died within a minute of the examination. A diagnosis of cerebral hemorrhage in the region of the fourth ventricle was made on the basis of the absence of any lesions of the cranial nerves or signs of destruction of the pyramidal tracts, and the rapidity of death.

Autopsy.—On incision of the dura a moderate amount of blood-tinged cerebrospinal fluid escaped. The pia over the entire vertex showed grayish yellow exudate, which was most marked along the large veins, especially over the anterior two thirds of the brain. An extensive hemorrhage covered the entire right cerebellar lobe (fig. 6*A*), especially on its mesial surface, and pressed on the medulla.

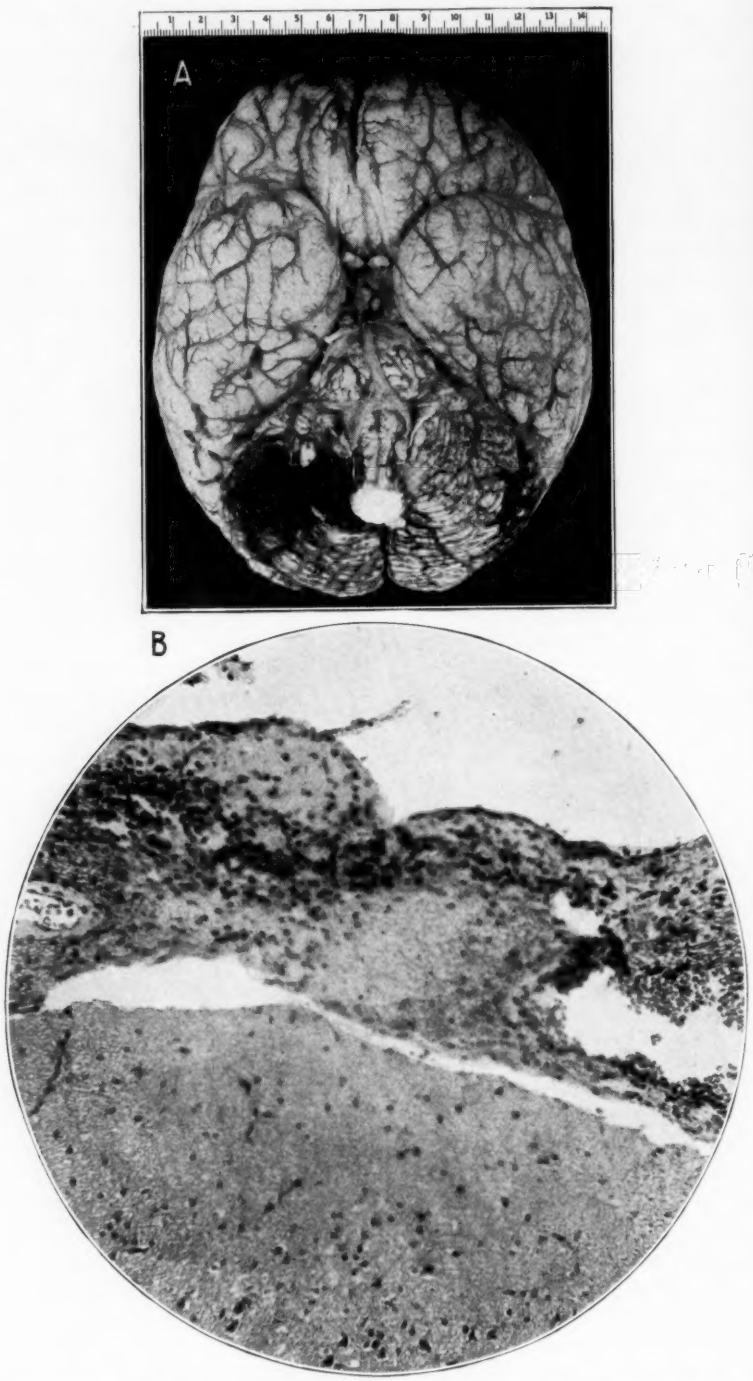

Fig. 6.— *A*, pia-arachnoid hemorrhage pressing on the medulla. *B*, infiltration of pia with polymorphonuclear leukocytes and red blood cells. × 125.

The ventricles of the brain were free from blood. The sinuses of the skull were opened and found to be normal. A smear of the pial exudate showed a gram-positive diplococcus. Microscopic sections revealed infiltration of the pia with polymorphonuclear leukocytes and red cells (fig. 6*B*). The neurocytes showed cloudy swelling, chromatolysis and neuronophagia. No inflammatory reaction was present. In addition, autopsy disclosed lobular pneumonia (streptococcic), hemorrhages in the stomach, acute infectious splenomegaly, cloudy swelling of the liver, cloudy swelling of the kidneys with focal necrosis and diffuse hemorrhage of the adrenal glands. The sudden death was due to the subarachnoid hemorrhage, which pressed on the medulla. The bronchopneumonia and the suppurative meningitis were probably of hematogenous infection, occurring during prolonged labor in a patient with low resistance.

Case 3.—L. S., a white woman aged 32, was admitted to the Jewish Hospital on Oct. 18, 1931 and was discharged on November 8. On October 17 she experienced a cramplike sensation in the right side of the abdomen and pain in the jaws. She began to vomit. The pain and vomiting persisted, and she was sent to the hospital, where examination disclosed tenderness and spasm in the right lower quadrant of the abdomen. The blood count showed 19,400 white cells, with 93 per cent polymorphonuclears. An appendectomy was performed, and the condition proved to be acute gangrenous appendicitis. Operation was performed, with the patient under spinal anesthesia. The surgeon noted the uniformly blood-tinged spinal fluid, which he recognized as differing in appearance from the usual bloody spinal fluid caused by trauma of the spinal puncture needle. On October 19 the patient experienced pain in both lower jaws. On October 20 herpes appeared on the left side of the lip and the left side of the hard palate. On October 22 the headache and vomiting returned. On October 23 she presented definite rigidity of the neck and a Kernig sign. On that day she complained of severe headache and of pain in the small of the back. The pupils were equal and reacted well. The eyegrounds showed vascular engorgement. There were loss of deep reflexes and loss of the right plantar reflex. On spinal puncture a bloody fluid under increased pressure was collected in several test tubes. The herpes was still present on the left side of the upper jaw and on the left side of the upper lip. The patient continued to improve and was finally discharged, apparently in satisfactory condition.

She was seen again on Nov. 14, 1933, seeking help for episodic headaches, which had persisted since her discharge from the hospital. She described the pain as beginning in the left side of the lower jaw, radiating upward to the back of the head and gradually spreading over the entire head. The results of neurologic examination were normal in every respect. It is quite apparent that the patient suffered from a generalized infection, which was responsible both for the appendicitis and the herpes and which caused changes in the pial vessels, producing bleeding.

Case 4.—M. G., a girl aged 1 year, was admitted to the Kingston Avenue Hospital on Feb. 18, 1941 and died on February 22. She was born prematurely, at 7 months, and weighed 2½ pounds (1,134 Gm.) at birth. Her weight on admission was 7 pounds (3,175 Gm.). On Nov. 11, 1940 she began to have paroxysmal coughing, and a diagnosis of whooping cough was made. On the day before admission convulsions appeared. On admission she was undernourished and in semicoma. There were purulent discharge from the nose and rales on the left side of the chest. The roentgenogram did not disclose any evidence of deposition of heavy metals in the ends of the long bones. The epiphyses and

the long bones were well developed and were normal. There was no clinical indication of scurvy, rickets or syphilis. There were 4,200,000 red cells, 48 per cent hemoglobin and 13,100 white cells, with 73 per cent polymorphonuclears. The spinal fluid was clear and contained 35 mg. of total protein per hundred cubic centimeters. On February 20 the patient again had a convulsion and there was definite rigidity of the lower extremities. There was marked pallor of both nerve heads. The veins appeared tortuous. The margins, however, were clear. Kernig and Babinski signs were present bilaterally. Spinal puncture revealed bloody spinal fluid. The temperature was 103 F. on admission, and it gradually increased to 104 F. and remained so until February 21, when it rose to 106 F. The patient died on February 22.

Necropsy disclosed extensive hemorrhages covering the upper surface of both hemispheres, especially in the anterior two thirds, more on the left side of the vertex than on the right, and the entire base of the brain was covered by hemorrhagic exudate. The left frontal and parietal lobes appeared very soft and mushy. Sections of the brain showed a hemorrhagic, soft condition of the entire corona radiata, the basal ganglia and the thalamus. Microscopically, numerous hemorrhages were seen surrounding the small capillaries, and many of these hemorrhages became confluent. The endothelial lining of the capillaries appeared cloudy. The neurocytes showed marked cloudy swelling and extensive chromatolysis.

Subarachnoid Hemorrhage Due to Rupture of Intracranial Aneurysm.—Aneurysms of the cerebral vessels have received considerable attention in the past two decades.[15] They generally occur in and about the circle of Willis, especially at the junctions of two or more vessels.[16] They are usually classified as (1) congenital, due to a developmental defect of the muscularis of the media and degeneration of the elastica;[17] (2) arteriosclerotic, due to atheromatous changes in the vessels, and (3) mycotic, secondary to an inflammatory process in the vessel wall. Generally the aneurysm is recognized after it has ruptured. Angiography[18] has made it possible to recognize the presence of some aneurysms before they rupture. Careful analysis of the roentgenograms of the skull[19] may

15. (*a*) Sands, I. J.: Aneurysms of the Cerebral Vessels, Arch. Neurol. & Psychiat. **21**:37 (Jan.) 1929. (*b*) Symonds, C. P.: Contributions to the Study of Intracranial Aneurysms, Guy's Hosp. Rep. **73**:139 (April) 1923. (*c*) Parker, H. L.: Aneurysms of Cerebral Vessels, Arch. Neurol. & Psychiat. **16**:728 (Dec.) 1926. (*d*) Hassin, G. B.: The Pathogenesis of Cerebral Hemorrhage, ibid. **17**: 770 (June) 1927. (*e*) Sweet, W. H.: Seeping Intracranial Aneurysm Simulating Neoplasm, ibid. **45**:86 (Jan.) 1941. (*f*) Richardson, J. C., and Hyland, H. H.: Intracranial Aneurysms, Medicine **20**:1 (Feb.) 1941.

16. McDonald, C. A., and Korb, M.: Intracranial Aneurysms, Arch. Neurol. & Psychiat. **42**:298 (Aug.) 1939.

17. Forbus, W. D.: On the Origin of Miliary Aneurysms of the Superficial Cerebral Arteries, Bull. Johns Hopkins Hosp. **47**:239 (Nov.) 1930.

18. Gross, S. W.: Cerebral Arteriography by Means of a Rapidly Excreted Organic Iodide, Arch. Neurol. & Psychiat. **44**:217 (July) 1940.

19. Sosman, M. C., and Vogt, E. F.: Aneurysms of Internal Carotid Artery and Circle of Willis from Roentgenological Viewpoint, Am. J. Roentgenol. **15**:122 (Feb.) 1926.

disclose confirmatory evidence of the presence of the aneurysm as manifested [20] in a curvilinear shadow above and to one side of the sella turcica, unilateral erosion of the sella turcica, enlargement of the sella unilaterally and of the optic foramen and sphenoid fissure or displacement of the pineal gland. Moreover, careful perimetry [21] may disclose visual field defects due to compression of the optic chiasm, the optic nerves or the optic tracts. The aneurysm may rupture directly into the subarachnoid space or may burrow itself into the adjacent brain tissue, and may even rupture into one of the horns of the ventricles. There are many [15f] who believe that in a vast majority of cases subarachnoid hemorrhage is caused by a ruptured aneurysm. The signs and symptoms of ruptured aneurysm are (1) those due to the causes of the formation of the aneurysm, (2) those due to pressure on surrounding structures of the brain and (3) those due to subarachnoid bleeding. Twenty-five patients with subarachnoid hemorrhage caused by ruptured intracranial aneurysm were present in our series. Of these, 12 died and 13 recovered. One had a recurrence of subarachnoid bleeding after an interval of thirteen years, during which she enjoyed relatively good health. In this particular case the question of syphilis was raised. On the first admission [15a] the Wassermann reaction of the blood was positive; on the second admission the Wassermann reactions of the blood and spinal fluid were both negative. On the whole, it may be said that syphilis plays no role in the causation of aneurysm or of subarachnoid hemorrhage.

The following cases are illustrative.

Case 1.—W. B., a man aged 44, the father of 6 children, was admitted to the Jewish Hospital on April 5, 1929 and was discharged on April 22, 1929. The patient had been having frequent headaches for the past two weeks and pain radiating from the back of the head to the thighs. On April 2, while at work as a blacksmith, he felt as if some one had struck him with a hammer on the back of the head. He fainted and was unconscious for two to three minutes and vomited. The headache and vomiting persisted. Examination on admission to the hospital showed irregularity of the pupils, particularly of the right, which reacted sluggishly. Examination of the fundi showed marked retinal arteriosclerosis and slight blurring of the margins of the disks. There were rigidity of the neck and a moderate Kernig sign bilaterally. The knee jerks were present, and there was an equivocal Babinski reflex on the right. The abdominal reflexes were present. The temperature was 100 F. The blood pressure was 144 systolic and 94 diastolic. The urine was normal. The blood count showed 13,600 white cells, with 67 per cent polymorphonuclears. The spinal fluid was under moderately

20. McKinney, J. M.; Acree, T., and Soltz, S. E.: The Syndrome of the Unruptured Aneurysms of the Intracranial Portion of the Internal Carotid Artery, Bull. Neurol. Inst. New York **5**:247 (Aug.) 1936.

21. Jefferson, G.: Compression of the Chiasma, Optic Nerves, and Optic Tract by Intracranial Aneurysms, Brain **60**:444 (Dec.) 1937.

increased pressure and was bloody. Repeated spinal punctures relieved his headache, and his condition generally improved, so that he was finally discharged. He was readmitted on March 10, 1931, with the history that he had been ill in bed for a week with a cold and "grip" and that he had suddenly experienced a severe headache the previous day and vomited. Examination showed rigidity of the neck and a marked Kernig sign bilaterally. The pupils were unequal, the left being larger than the right, and both were fixed to light and in accommodation. The eyegrounds showed engorgement of the veins. The deep reflexes were absent, and the abdominal reactions were lost. The temperature was 102 F., the pulse rate 90 and the blood pressure 160 systolic and 90 diastolic. Two hours after admission, while talking to the nurse, he suddenly threw up his hands and sank into coma. His body was limp, and there were no signs of meningeal irritation. He died at 4 a. m. on March 11.

Autopsy.—On removing the dura free blood was seen at the base of the brain, which weighed 1,425 Gm. The brain was edematous; the convolutions were broad, and the sulci were practically obliterated. A large hemorrhage involved the entire base of the brain, being most marked in the anterior half. At the junction of the right anterior cerebral and the anterior communicating artery was an oval aneurysm, measuring 1 by 0.5 cm., which showed a small rent in its ventral portion and was surrounded by an organized clot. Section of the fixed brain disclosed a hemorrhage which filled the entire ventricular system, particularly the left frontal horn, where the adjacent brain tissue was disrupted by the hemorrhage. Microscopic sections of the aneurysm revealed irregularity in its various layers, the media especially being thin and degenerated. In a few areas the media was entirely absent. The elastic layer was split and reduplicated. The intima showed irregular thickening. At the point of rupture the layers were extremely thin. In one portion of the aneurysm there was an organized blood clot. The pia-arachnoid showed a marked fibroblastic reaction, with extravasated blood in its meshes. It contained numerous macrophages. The neurocytes showed cloudy swelling and neuronophagia. Adjoining the left anterior horn of the lateral ventricle the brain tissue showed numerous hemorrhagic areas, which had become confluent in several places. The capillaries showed the characteristic appearance seen in a few cases in which the patient died of clinical "influenza," viz., infiltration of the walls with lymphocytes and plasma cells and a large zone of hemorrhage surroundnig these capillaries. Sections from the basilar artery showed no particular change.

The rest of the autopsy disclosed adhesvie pleuritis on the right, pulmonary atelectasis and emphysema, bilateral bronchopneumonia, cardiac hypertrophy and dilatation, fatty degeneration and chronic passive congestion of the liver, nephrosclerosis and subacute glomerular nephritis, acute splenomegaly and congestion and fibrosis of the pituitary gland.

Obviously, the subarachnoid hemorrhage in 1929 was due to leaking of the aneurysm. The recent illness was due to an acute infection (influenza?), which was complicated by confluent cerebral hemorrhages and resulted in a fatal intraventricular hemorrhage.

Case 2.—M. V., a white woman aged 42, was admitted to the Jewish Hospital on Feb. 8, 1932 and died two hours after admission. On the evening of February 4 she had a seizure, foamed at the mouth and fell to the floor. She was put to bed and on regaining consciousness complained of headache. She remained in bed after this incident, complaining of headache and vomiting occasionally. On the morning of February 8 her husband returned from his work as a night watchman and found her unconscious and bleeding from the nose. She was taken to

the hospital in a comatose condition. There was weakness of the right side of the face. The pupils were dilated. A large fresh hemorrhage covered the left disk. The blood pressure was 70 systolic and 50 diastolic. The temperature was 103 F. The pulse was barely perceptible, and she died soon after entering the hospital.

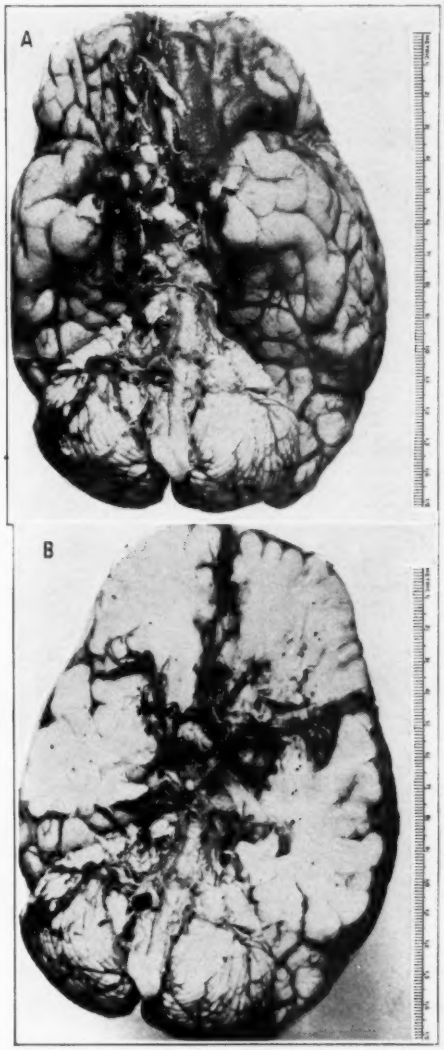

Fig. 7.—*A*, hemorrhage at the base of the brain caused by ruptured aneurysm. *B*, aneurysm at the junction of the left middle cerebral and the internal carotid artery.

Autopsy.—On section of the dura free blood escaped. The brain was soggy, and an extensive hemorrhage covered the entire base (fig. 7 *A*). At the junction of the internal carotid and the left middle cerebral artery was an aneurysm, 2 by

1.5 by 2 cm. (figs. 7 *B* and 8), which was deeply buried in the adjacent brain tissue, and an extensive hemorrhage invaded the adjoining cerebral cortex. There was a small aneurysm, 8 by 5 mm., of the anterior communicating artery. The posterior communicating arteries were very thin and narrow, and the right showed a peculiar irregular appearance in that there were numerous small, thin vessels in an anastomotic arrangement. The walls of the other branches of the circle of Willis showed an irregular outline. Microscopically, the walls of the posterior

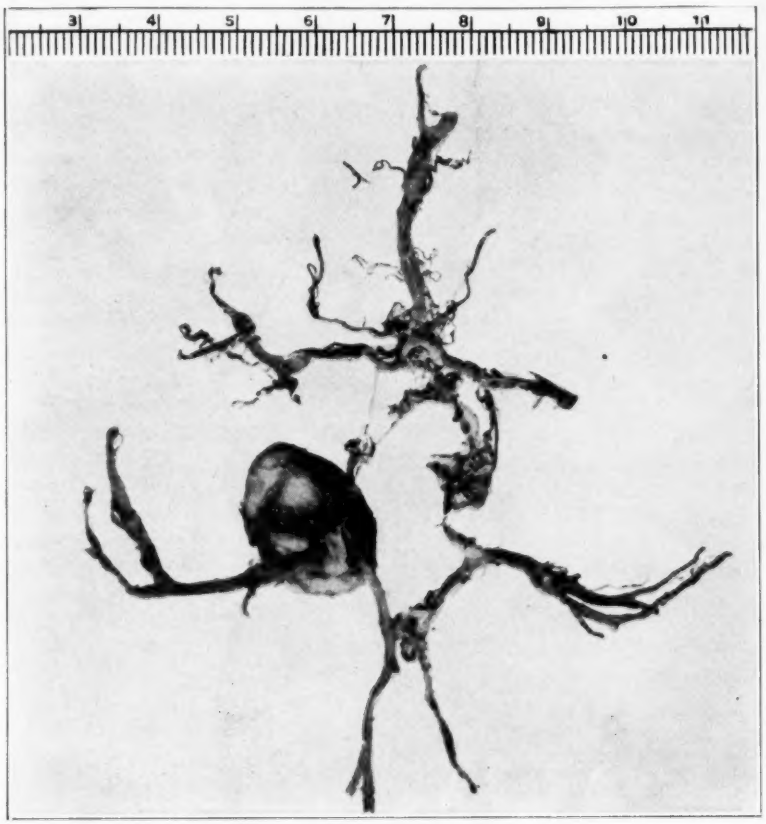

Fig. 8.—Multiple cerebral aneurysms.

communicating arteries were reduced to a mere endothelial layer. The other arteries showed irregularly arranged degenerative areas, with marked diminution of the muscular coat. The intima showed irregularly distributed proliferation and degeneration in several places. The brain tissue showed moderate edema. The neurocytes showed cloudy swelling and satellitosis. There was a moderate microglial and oligodendroglial reaction. The pia showed a hyperplastic reaction, with blood extravasations and numerous macrophages. In addition, autopsy showed lobular pneumonia and pulmonary edema, cloudy swelling of the viscera and ovarian cysts.

Subarachnoid Hemorrhage Secondary to Massive Cerebral Hemorrhage.—Massive cerebral hemorrhage [22] may extend into the adjacent subarachnoid space and result in signs of meningeal irritation and in bloody spinal fluid. As a rule patients with this condition have previously shown signs of cerebral arteriosclerosis. They may have had previous cerebral vascular insults. Occasionally, massive cerebral hemorrhage may result from confluent pericapillary hemorrhages occurring in the course of toxic states or of blood dyscrasias. The history usually points to the clinical picture of a hemorrhage into the brain tissue, with sudden signs of meningeal irritation. The bloody spinal fluid is corroborative evidence of the condition. There were 2 cases in our series in which such a condition was present. The following case is illustrative.

A. L., a white woman aged 26, married, was admitted to the Jewish Hospital on June 22, 1929 and died on June 24. One month prior to her admission to the hospital she complained of headache, nausea and vomiting. This continued until three weeks before admission to the hospital, when she suddenly became stuporous. She continued in this state for three hours and remained in bed for a week. Two days before admission to the hospital she again lost consciousness for several hours. On admission her pupils were widely dilated, the left more than the right, and both reacted well to light and in accommodation. The eyegrounds were swollen and the margins were indistinct, especially the left. Numerous small, irregular hemorrhages were seen in both retinas. She presented weakness of the right external rectus muscle and the right side of the face. There were paresis of the right upper extremity and a Babinski sign on the right. Her blood pressure was 110 systolic and 60 diastolic. The urine was normal. The blood count showed 11,200 white cells, with 81 per cent polymorphonuclears. The temperature was 101.4 F., the pulse rate 82 and the respiratory rate 22. A spinal puncture yielded bloody fluid. She was drowsy for a day and finally became stuporous and died.

Autopsy.—The dura was very tense, especially over the left frontoparietal region. On incising the dura free blood was found beneath it. The brain weighed 1,180 Gm. A large hemorrhage in the left frontal lobe compressed the left anterior horn of the ventricle. Microscopically, the meshes of the pia showed extravasation of blood. Numerous macrophages were present and contained blood pigment and debris. The pial vessels showed considerable thickening. Throughout the portion of the brain adjacent to the clot the capillaries showed definite fibrosis and were much thickened. Several were thrombosed. Numerous hemorrhagic areas were present in this region of the brain, and these zones became confluent in several places. There were numerous gitter cells in this region. There was a decided microglial and oligodendroglial reaction. No evidence of inflammation was present. In addition, autopsy showed pericardial fibrosis; acute congestion of the pituitary gland, lungs and liver, and cloudy swelling of the liver and kidneys.

Subarachnoid Hemorrhage Secondary to Intraventricular Hemorrhage.—Intraventricular hemorrhage [23] results from rupture of a vessel

22. Globus, J. H., and Strauss, I.: Massive Cerebral Hemorrhage, Arch. Neurol. & Psychiat. **18**:215 (Aug.) 1927.

23. Sands, I. J., and Lederer, M.: Intraventricular Hemorrhage, J. Nerv. & Ment. Dis. **65**:360 (April) 1927.

near the ventricular wall, from extension of the hemorrhage from a blood clot or from the rupture of an aneurysm into a ventricular horn. The acute onset of cerebral symptoms in a person who is known to have cerebral arteriosclerosis or is suspected of having intracranial aneurysm, with the early appearance of coma, persistent blood in the spinal fluid or the presence of repeated tonic spasms of the entire somatic musculature, or the early onset of complete flaccidity of all muscles, with the absence of classic signs of paralysis, should lead to the diagnosis of intraventricular hemorrhage. The temperature, as a rule, is high, and usually there is a fatal termination. In a person who is in coma and who is known to have had hypertension, cerebral arteriosclerosis or a previous cerebral vascular insult, a sudden and prompt elevation of temperature to 105 to 106 F. points to an intraventricular hemorrhage. This criterion has proved of frequent diagnostic aid. Three cases of this type have occurred in our series. The following 2 instances are illustrative.

Case 1.—A. R., a white woman aged 60, was admitted to the Jewish Hospital on Sept. 9, 1932 and died on September 11. According to the history given by her son, she had returned from church at 7 o'clock a. m. and told him that a peculiar sensation came over her while at church and she fainted. However, her condition was such that he did not think it serious, and he went to work at 9 a. m. On returning from work at 4:30 p. m. he found her unconscious on the floor, foaming at the mouth. He called an ambulance, and she was taken to the hospital. He said that three years ago she had a fainting spell and was unconscious for about an hour. Six months ago she had a similar attack while working in the kitchen. She fell and was unconscious for about two hours, but afterward was apparently well. Examination revealed a well nourished, elderly woman who was unconscious and had bloody foam about the lips. The pupils were unequal; the right was round and the left oval and almost pinpoint. There was flaccidity of the upper extremities and of the right lower extremity. The left lower extremity was somewhat spastic. All the deep reflexes were absent except for a faint knee jerk on the right. A Babinski sign was present bilaterally. Her temperature was 98.6 F. and her pulse rate 68. The urine gave a 2 plus reaction for albumin and contained hyaline and granular casts. The blood pressure was 120 systolic and 80 diastolic. The Wassermann reaction of the blood was negative. She continued in the unconscious state in which she was admitted. The temperature gradually rose, and she died.

Autopsy.—On deflection of the dura fresh blood was seen in the subarachnoid space. The brain weighed 1,475 Gm. There were fresh blood clots at the base, which covered the pons and medulla and filled the great cisterns. The basilar artery and the branches of the circle of Willis were uniformly sclerotic. The smaller vessels also appeared sclerosed. The surface of the brain appeared blood tinged, the convolutions were flattened and the fissures were compressed. Section of the brain disclosed a massive hemorrhage in the right thalamostriatal region and an intraventricular hemorrhage which filled all the ventricles on the right side as well as the third and fourth ventricles. Numerous thrombotic vessels were present in the right lenticular nucleus and in the right thalamus. Microscopically, the pia showed advanced fibrosis and thickening of long standing, with infiltration by macrophages and mononuclear elements. There was extravasation of blood in its meshes. The pial vessels were unusually thickened and were

engorged with blood. The brain adjacent to the blood clot showed considerable disruption by the numerous hemorrhages. There was marked thickening of the capillaries, many of them being thrombosed. The neurocytes were swollen and showed chromatolysis and neuronophagia. No inflammatory reaction was present. The medullary vessels were sclerosed. The basilar and all the larger branches of the circle of Willis showed advanced atheromatous changes involving all the constituent layers. There were replacement of the muscular coat by fibrous tissue and considerable hyaline and fatty degeneration in this layer. The intima was irregularly thickened, and the adventitia showed definite fibroblastic proliferation. The elastic layer showed an advanced degree of degeneration, with splitting and reduplication of the fibers. In addition, autopsy showed bronchopneumonia and pulmonary edema, cardiac hypertrophy and fatty degeneration of the liver and adrenal glands. There was no arteriosclerotic change elsewhere in the body.

CASE 2.—S. P., a woman aged 50, was admitted to the Jewish Sanitarium and Hospital for Chronic Diseases on Feb. 21, 1939 and died on Oct. 10, 1940. On Sept. 5, 1936 the patient slumped in a chair while eating her breakfast. She did not lose consciousness immediately. A physician was called, who said she had had a stroke. She soon became stuporous and remained so for two and a half weeks. She then became comatose and was taken to the Mount Sinai Hospital, where a blood clot was removed from the brain. She remained in the hospital for about five months. On admission to the Sanitarium the blood pressure was 220 systolic and 110 diastolic. A right craniotomy scar was present. She had pseudobulbar speech, left hemiplegia and left homonymous hemianopia. An Oppenheim reflex was present on the right. Hyperreflexia was noted on the same side. There was also evidence of moderate coronary disease. Her condition was unchanged until the day of her death, when she suddenly collapsed and died.

The following observations were made at necropsy: There was an effusion of recent blood over the ventral surface of the brain stem and the inferior surface of both cerebellar lobes (fig. 9 *A*). The medulla was widened and the vessels were markedly arteriosclerotic. At the junction of the pons and the medulla there was a firm mass of blood, which buried the nerves in that region. The vertebral arteries were unequal in size, the right being larger than the left. At the termination of the basilar artery, and leading into the left part of the interpeduncular space, there was an aneurysm (fig. 9 *B*), measuring ½ inch (1.27 cm.) in width and ¾ inch (1.91 cm.) in length. The entire ventricular system was filled with a recent extravasation of blood. At the left side of the third ventricle the blood occupied a defect in the cerebral substance extending laterally from the third ventricle to the globus pallidus of the left corpus striatum. The area of cerebral substance invaded by the blood clot measured 1 inch (2.54 cm.) laterally and ½ inch (1.27 cm.) anterodorsally. It was rectangular and was separated from the interpeduncular space by a thin layer of tissue, measuring 1/16 inch (1.5 mm.) in thickness. The blood clot had extended into the midbrain, where it occupied the left cerebral peduncle, the substantia nigra and part of the tegmentum. It had ballooned the left half of the midbrain in its lower part and extended over to the right side for a distance of 1 inch (2.54 cm.). There was blood in the aqueduct and in the fourth ventricle. The left putamen in its lower half was the seat of several elongated cysts. The latter occupied the entire ventrodorsal diameter of the putamen in a lesion the width of a string. There was no seeming destruction of the right internal capsule. The left internal capsule was occupied by the hemorrhage already described. The right half of the pons was smaller than the left. The right pyramid was much atrophied; the left was normal.

Coronal section through the posterior limb of the internal capsule revealed the following lesions: On the left side cysts occupied the putamen. The clot in the third ventricle and in the cerebral substance lateral to it pressed on the internal

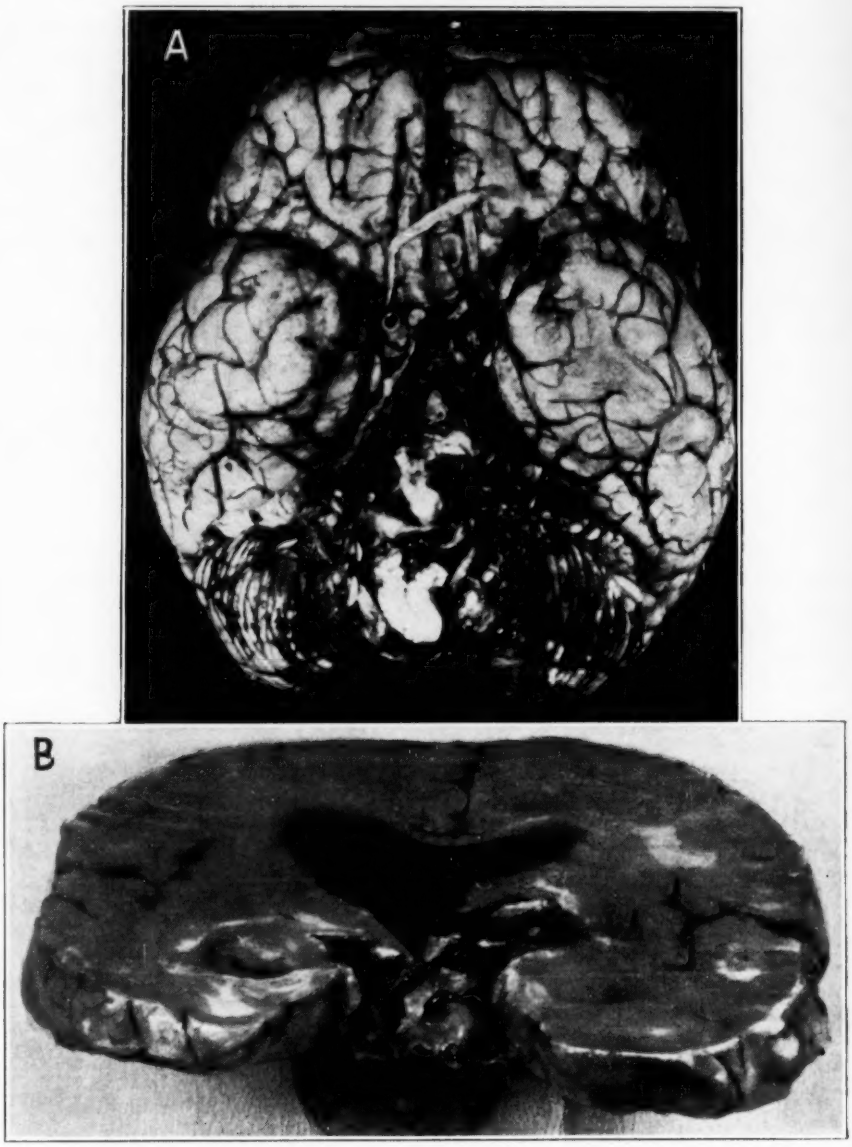

Fig. 9.—*A*, subarachnoid hemorrhage secondary to intraventricular hemorrhage. *B*, intraventricular hemorrhage. Note aneurysm of the superior cerebellar artery.

capsule. In the lower portion of this clot was the aneurysm previously described. It was well circumscribed, was laminated and measured 1 cm. in diameter; it was located entirely on the left side. On the right side were atrophy of the internal

capsule with golden brown pigment, atrophy of the posterior part of the putamen, dilatation of the body of the lateral ventricle and extension of the clot in the third ventricle laterally into the internal capsule. There was blood in both inferior horns. The point of rupture of the intraventricular hemorrhage was in the left posterior perforated substance.

The diagnoses were as follows: massive intracerebral hemorrhage; intraventricular hemorrhage; aneurysm of the left superior cerebellar artery; old atrophy of the right pyramidal tract; old lesion in the right internal capsule; cysts in the left putamen.

Subarachnoid Hemorrhage Due to Blood Dyscrasias.—Subarachnoid hemorrhage may be encountered in cases of blood dyscrasias that are characterized by bleeding into the various body tissues and organs. The hemorrhage may occur in the brain tissue proper, and it may extend to the subarachnoid space or to portions of the ventricles. Occasionally the hemorrhage may be limited to the subarachnoid space, and not infrequently it may become encapsulated, with signs of meningeal irritation but without bloody spinal fluid. Four cases in our series belong to this category, the primary diseases being aplastic anemia, aleukemic leukemia, agranulocytic leukemia and thrombocytopenia respectively. All the patients died.

The following case is illustrative.

L. K., a white man aged 44, was admitted to the Jewish Hospital on March 11, 1937 and died on March 15. He had had three previous admissions to the hospital since Feb. 13, 1937 for the purpose of receiving blood transfusions for aleukemic leukemia. He had apparently been in good health until two years before admission, when he began to suffer from progressive anemia. In all he had had twenty-five blood transfusions in the preceding two years. After the last admission chill and fever developed, followed by hemorrhagic manifestations. He had subconjunctival hemorrhages, as well as retinal hemorrhages and hemorrhages from the gums. There were numerous petechial hemorrhages on the skin. He also had definite nuchal rigidity and unequal pupils, the left being larger than the right. There was right hemiplegia, with hyperreflexia, a Hoffmann sign and a Babinski sign on the right side. He was in coma, from which he could not be aroused. Bloody spinal fluid was obtained. He died on March 15. Permission for autopsy was not obtained.

Subarachnoid Hemorrhage Due to Cerebral Vascular Neoplasm.—A vascular cerebral neoplasm may cause subarachnoid bleeding and produce a clinical picture presenting considerable difficulty in diagnosis.[24] Four patients in our series had such a condition, and of these 3 died and 1 is still alive.

The following cases are illustrative.

Case 1.—F. T., a white, married woman aged 38, was admitted to the Jewish Hospital on June 5, 1932 and was discharged on June 15. She was in good health

24. Cohen, I.: Neoplastic Cysts Communicating with the Lateral Ventricles, Bull. Neurol. Inst. New York **5**:21 (Aug.) 1936.

until June 2, when she complained of headache. The headache was at first located in the right eyeball and in the right temple and was not relieved by ordinary medication. It increased in intensity and was associated with vomiting. On admission to the hospital she showed weakness of the left upper extremity. The pupils were in middilatation, and the eyegrounds showed marked myopia but no other changes. There was marked rigidity of the neck, and on spinal puncture 25 cc. of xanthochromic fluid was removed. The urine showed a faint trace of albumin. The blood count was 3,900,000 red cells, 65 per cent hemoglobin and 8,000 white cells, with 68 per cent polymorphonuclears. The temperature was 100 F. and the pulse rate 50. The chemical constituents of the blood were normal. On June 8 she became comatose, and at that time absence of the knee jerk and ankle jerks on the left side was noted. There was also weakness of the left facial nerve of supranuclear type. The Babinski sign was elicited bilaterally. There were no pupillary disorders. On June 9 she was cooperative. She then complained bitterly of headache. There was marked rigidity of the neck. Flaccid paralysis was present on the left side, including all the muscles of the left side of the face. There was a bilateral Babinski sign, more marked on the left side. Sensation was apparently intact. It was difficult to test for hemianopia or astereognosis, as the patient would not cooperate. The spinal fluid was under moderately increased pressure and was bloody. Her temperature rose to 101 F., and the pulse rate varied between 60 and 64. She remained in the hospital until June 15, when there was considerable improvement in the hemiplegia, and at that time there was no evidence of hemianopia. She was seen on July 25, when she complained of headache. The gait and station were ataxic; there were diplopia on looking to the right and hyperesthesia and hypalgesia over the left side. The eyegrounds could be seen with a —15 lens, and they appeared edematous. On September 12 the headache became intense. She was nauseated, vomited and complained of pain in the back of the head and in both shoulders. The headache and vomiting persisted, and on September 19 she was readmitted to the hospital. She was excited and complained bitterly of headache. The pupils were unequal, the right being larger than the left, and both reacted sluggishly. The eyegrounds at that time did not show any evidence of papilledema. All the deep reflexes were absent in the lower extremities and were sluggish in the upper extremities. There was paralysis of the left sixth nerve. A spinal puncture resulted in clear fluid, under a pressure of 500 mm. of water. The fluid contained few red blood cells; the total protein content was 47 mg. per hundred cubic centimeters. The Wassermann reaction was negative. A diagnosis of vascular tumor in the right supratentorial region was made. She was removed from the hospital, against advice, on September 30. A few days later Dr. Ira Cohen was consulted, and the diagnosis of an intracranial neoplasm was made. She was sent to the Mount Sinai Hospital as an emergency case, and a right subtemporal decompression was performed. The edge of the tumor was seen projecting from beneath the temporal lobe. Two days later a flap was turned down, and a large part of the tumor was enucleated. She eventually died; at autopsy the tumor was found to extend into the right occipital lobe and was reported as a hemangiosarcoma. It is noteworthy that on the first admission to the hospital this patient showed signs of a subarachnoid hemorrhage. The question of a neoplasm had not been considered. On the second admission, however, it became apparent that the increasing headache and the spinal fluid pressure pointed to a cerebral tumor, and the diagnosis accordingly was made.

CASE 2.—H. B., a white man aged 29, was admitted to the service of Dr. J. Ramsay Hunt at the Neurological Institute of New York on Oct. 26, 1933 and died on October 29. The patient complained of headache, vertigo, vomiting, nausea, a sensation of falling, stiffness of the neck, disturbance of vision and drowsiness. Six years before he had similar symptoms, which occurred suddenly and lasted three of four weeks. This condition cleared up spontaneously without specific treatment. A similar attack occurred one year before and lasted equally long. The third attack occurred on Oct. 20, 1933, the symptoms appearing in the order listed. A physician, called at the time, noted a tendency to fall to the left and marked ataxia in the left extremities. On admission to the hospital the patient was drowsy and uncooperative and held his head slightly in opisthotonos and to the left. Nonequilibratory tests showed ataxia in the left extremities. Succession movements were poorly performed with the left extremities. Speech was slurring and retarded. The reflexes were active and the patellar reflexes somewhat exaggerated. There were no pathologic reflexes. The abdominal reactions were sluggish on the right side. There were marked rigidity of the neck and a mild Kernig sign. Generalized muscular weakness was present. No sensory changes were found. The fundi showed blurring of the upper and nasal margins of the disks. The pupils were circular and slightly irregular; the right reacted promptly, while the left responded sluggishly to light and in accommodation. There were coarse nystagmus to the left and loss of conjugate deviation to the left. There were dyssynergy and dysmetria in the upper extremities, more marked on the left side. Percussion of the skull caused severe headache. The spinal fluid on October 28 was yellow and showed 682 red cells, a 1 plus reaction for globulin, 48 mg. of protein per hundred cubic centimeters and a negative Wassermann reaction. On October 29 the spinal fluid was yellow, contained 1,296 red blood cells and 50 mg. of protein and gave a 1 plus reaction for globulin. The urine showed a very faint trace of albumin and rare hyaline casts. The roentgenogram of the skull was normal. Two days after admission the signs of increasing meningeal irritation appeared and the spinal fluid showed evidence of recent hemorrhage. The temperature rose suddenly, and the patient died.

Autopsy was performed by Dr. Abner Wolf, who found a vascular tumor (angioma) occupying the left half of the vermis and the left cerebellar lobe, the hemorrhage resulting from a tear in the inferior and lateral surfaces of the left cerebellar lobe.

TREATMENT

In the management and treatment of patients with subarachnoid hemorrhage, it is hoped that the following objectives are to be obtained: (1) the relief of headache; (2) the reduction of increased intracranial pressure; (3) the control of excitement; (4) proper feeding; (5) the institution of surgical procedure whenever indicated, and (6) the rehabilitation of the patient.

It is best to have the patient in a hospital where constant and adequate medical and nursing care are obtainable.

Headache is a common and a most distressing complaint in all cases. In the average case mild sedatives, such as codeine in combination with acetylsalicylic acid, may suffice. Occasionally chloral hydrate and the barbiturates may be employed. Morphine should never be given. Eleva-

tion of the head of the bed aids the hydrodynamics of the cerebrospinal fluid circulation and sometimes tends to relieve headache.

For the reduction of increased intracranial pressure, hypertonic solutions of dextrose or of sucrose have proved efficacious in many instances. Magnesium sulfate, given intramuscularly, may be employed. Caffeine with sodium benzoate, especially for comatose patients, has been valuable. There is considerable difference of opinion regarding the value of lumbar puncture for these patients. One school of thought advises it in almost every instance, while another takes a diametrically opposite point of view. There is no doubt that lumbar puncture relieves headache and reduces intracranial pressure in many patients. I have seen prompt relief from headache by lumbar puncture when other methods have failed. Furthermore, the removal of bloody fluid tends in a measure to prevent the deleterious effects on the brain produced by such fluid, as shown experimentally in animals by Bagley.[25] However, this measure should be used judiciously, and only in cases of subarachnoid hemorrhage of traumatic and arteriosclerotic origin and in the group in which the cause is as yet unknown. In all other instances lumbar puncture should be performed only as a diagnostic procedure. This is particularly true in cases of subarachnoid hemorrhage due to a ruptured aneurysm, for repeated lumbar punctures in this group will jeopardize the patient's life. Increasing experience has taught me to remove only a small amount of spinal fluid at any one time, 5 to 10 cc., even in those cases in which this procedure is indicated. The limitation of fluid intake to 1,200 cc. per day in the average case has become an almost routine procedure.

Excitement has occurred in a considerable number of cases and has presented a serious problem. It tends to increase bleeding and, moreover, offers administrative difficulties. Paraldehyde, given by rectum, by mouth or, preferably, by intramuscular injection, has proved the drug of choice in allaying excitement. Occasionally sodium amytal, given intravenously, may be employed; however, this drug should be injected very slowly, and at least ten minutes should be taken for injection of the average dose of 5 to 7½ grains (0.3 to 0.48 Gm.). At times mild restraint, such as a sheet across the abdomen or a dry pack, may be employed. I have had a few cases in which the administration of salt, dextrose and large doses of vitamin B complex have helped to quiet the patient.

It is imperative that these patients receive an adequate amount of proper food. Feeding may sometimes present a serious problem. The vast majority of them have poor appetites; a few may vomit for a long

25. Bagley, C., Jr.: Blood in Cerebrospinal Fluid: Resultant Functional and Organic Aberration in the Central Nervous System, Arch. Surg. **17**:18 (July) 1928.

period; others show varying degrees of disturbance of consciousness, while many cannot take sufficient nourishment, without being able to explain their reluctance to take food. It is important to give them a sufficient amount of calories and, particularly, of salt and vitamins. It is sometimes necessary to resort to tube feeding. I have become convinced that some of the mental symptoms encountered in these patients are due to insufficient amounts of proper food. There is reason to believe that a few of the cases of Korsakoff's psychosis [26] occurring in the course of subarachnoid hemorrhage may be due to avitaminosis resulting from improper nourishment.

In recent years neurosurgical [27] measures have been instituted in treatment of patients with subarachnoid hemorrhage due to aneurysmal ruptures. Compression of the internal carotid artery in the neck followed by ligation of the vessel has been employed.[28] However, this procedure has not proved as effectual as had been anticipated. Cases of wiring and electrothermic coagulation of an aneurysm of the internal carotid artery within the skull have been reported.[29] Cases have also been reported in which a craniotomy is performed, the aneurysm exposed, its neck obliterated by placing a silver clip over it and its sack obliterated by electrocautery.[30]

To rehabilitate the patient, it is important to impress on him the necessity of remaining in the hospital for at least four to six weeks and to convince him of the need for a convalescent period of at least three to six months. I have known patients who have left the hospital and died within a few weeks because of some physical exertion or emotional excitement. It is necessary to prevent the occurrence of constipation in these patients. Coitus should be forbidden for several months. These patients should be taught to assume a philosophic attitude toward life and to avoid emotional tensions resulting from disappointments.

SUMMARY AND CONCLUSIONS

Subarachnoid hemorrhage is due to the presence of blood in the subarachnoid space and is a symptom, not a disease entity. While in some cases the causes are yet undetermined, in the vast majority of

26. Tarachow, S.: The Korsakoff's Psychosis in Spontaneous Subarachnoid Hemorrhage, Am. J. Psychiat. **95**:887 (Jan.) 1939.

27. Walsh, M. N., and Love, J. G.: Intracranial Carotid Aneurysms: Successful Surgical Treatment, Proc. Staff Meet., Mayo Clin. **12**:81 (Feb. 10) 1937.

28. Schorstein, J.: Carotid Ligation in Saccular Intracranial Aneurysms, Brit. J. Surg. **28**:50 (July) 1940.

29. Werner, S. C.; Blakemore, M. D., and King, B. G.: Aneurysm of Internal Carotid Artery Within the Skull: Wiring and Electrothermic Coagulation, J. A. M. A. **116**:576 (Feb. 15) 1941.

30. Dandy, W. E.: Intracranial Aneurysm of the Internal Carotid Artery Cured by Operation, Ann. Surg. **107**:654 (May) 1938.

instances the hemorrhage is due to trauma, arteriosclerotic degeneration of vessel walls, septic or infectious embolism, ruptured intracranial aneurysm, massive cerebral hemorrhage, intraventricular hemorrhage, blood dyscrasias or vascular cerebral neoplasm.

The syndrome is characterized by nuchal rigidity, a mild Kernig sign, hyperemia of the disks, mild leukocytosis, mild elevation of temperature, slow pulse and bloody spinal fluid. Symptoms referable to irritation of certain parts of the nervous system may be present. The onset is usually sudden and generally after some physical exertion or emotional excitement. Occasionally a prodromal period of symptoms may occur.

A series of 120 hospital-treated patients are presented, the youngest of whom was 3 weeks and the oldest 75 years of age. Fifty-five were females and 65 males. The condition in 27 was of unknown origin; in 30 it was due to arteriosclerotic degeneration of the vessel walls, in 9 to trauma, in 25 to ruptured intracranial aneurysm and in 16 to the action of bacteria or their toxins on small capillaries; in 2 it was secondary to massive cerebral hemorrhages, in 3 it followed intraventricular hemorrhages, in 4 it was caused by a blood dyscrasia, and in 4 it accompanied a vascular cerebral neoplasm. Of these 120 patients, 41 died and 79 recovered.

Treatment is directed toward the relief of headache, the reduction of intracranial pressure, allayment of excitement, adequate feeding, consideration of surgical measures in suitable cases of aneurysmal rupture and rehabilitation of the patient.

Illustrative cases are reported.

202 New York Avenue.

ABSTRACT OF DISCUSSION

Dr. Irving J. Sands, Brooklyn: The question of rehabilitating the patient after he leaves the hospital is important. Absolute rest is essential. All physical and emotional tensions should be eliminated. He should be told from what he is suffering and that he must rest. My associates and I now keep such patients in the hospital for six weeks. We tell the family precisely what may be expected.

Two ocular signs have impressed me. The first concerns the nerve head, not so much the hemorrhage as the fact that the center of the disk is more elevated than the periphery, and the second the pupillary disturbances. The latter I have found to be common, particularly in cases of the so-called indeterminate type and in those of hemorrhage due to arteriosclerotic degeneration. One never finds the pupils the same on two consecutive days. They change; they vary in size and shape within twenty-four hours, and I have found this variation a valuable sign.

Dr. Sigfried Baumoel, Cleveland: Dr. Sands objects to the term "spontaneous subarachnoid hemorrhage," believing that the term "spontaneous" is both misleading and meaningless. To be sure, the term as used here and in connection with other conditions could not bear close scrutiny, because nothing in this world

happens spontaneously. There is a cause for everything. However, I believe that the term "spontaneous subarachnoid hemorrhage" carries the implication of a clinical concept and designates a clinical and pathologic entity.

By spontaneous hemorrhage is understood a massive extravasation of blood into the subarachnoid space which is not caused by external injury and does not occur in the course of a blood dyscrasia or other focal or systemic disease; neither is included in this category the common intercerebral apoplexy, in which blood finds its way into the subarachnoid space by a rupture into the ventricles or through the brain substance. The effusion of blood into the subarachnoid space in the conditions last mentioned is merely a complication and constitutes simply an incident in a sequence of pathologic events, generally, if not always, the last. Such subarachnoid bleeding is a complication of some other condition, usually overshadowed by the symptoms of the primary disease, and as a rule receives little attention, either diagnostically or therapeutically. The spontaneous, or if I may say primary, subarachnoid hemorrhage, according to most authorities, is caused by the rupture of a small or miliary aneurysm at the base of the brain and presents an entirely different clinical picture.

There are a few conditions in the entire realm of neuropathology in which, in the absence of any recognized provocative factor, a person is struck out of a clear sky by a sudden severe headache with just as sudden signs of meningeal irritation. This condition, descriptions of which have at last penetrated into the modern textbooks on neurology, can in many instances be diagnosed even before the incriminating blood in the spinal fluid is obtained.

Dr. Sands has thoroughly and ably presented the symptomatology of subarachnoid hemorrhage. Focal signs, such as hemiplegia, hemianesthesia and hemianopia, due to the presence of blood in the subarachnoid space are rare and form an important differential feature in favor of an intracerebral hemorrhage. Globus and Strauss found hemiparesis in only 1 of a series of 34 cases, and my associates and I have found it only once in over 60 cases.

I should like to mention one point because of its almost pathognomonic significance, and that is the massive intraocular hemorrhage which is either subretinal or preretinal and which in some instances breaks through into the vitreous, filling a greater or a smaller portion of the posterior chamber of the eye. This is a rather infrequent sign, but if present it is strong evidence of the rupture of a blood vessel at the base of the brain in the close vicinity of the optic nerve.

As regards the prognosis of subarachnoid hemorrhage, I may say briefly that the great majority of patients recover from the first attack but that recurrences are common and many die during the second or during a subsequent attack.

As regards treatment, we employ frequent punctures, the indication for this procedure being severe headache, advancing papilledema and slow pulse. It is to be emphasized, however, that the fluid should be removed very slowly with the aid of a manometer.

THE SYMPATHETIC NERVOUS SYSTEM

INFLUENCE ON SENSIBILITY TO HEAT AND COLD AND TO CERTAIN TYPES OF PAIN

OLAN R. HYNDMAN, M.D.
AND
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IOWA CITY

In a previous communication [1] we called attention to the fact that the sensation from a sympathectomized zone of skin when exposed to cold differs considerably from that of a normally innervated zone. Seven patients were taken into a refrigerator at a temperature of 0 to 4 C. The patients were nude except for a loin cloth. They remained in the refrigerator from thirty to sixty minutes while studies of cutaneous temperature were carried out. Three patients had had a unilateral cervicodorsal ganglionectomy (removal of the inferior cervical and upper two dorsal ganglia). One had had unilateral removal of the inferior cervical and upper six dorsal ganglia. Two patients had had a unilateral splanchnicotomy and removal of the first and second lumbar ganglia. One patient had had bilateral removal of the second, third and fourth lumbar ganglia.

These patients volunteered the information that the sympathectomized zone did not feel the same as the opposite side or the remainder of the body. The difference was in relation to the sensation of cold and to the aching and stinging pain which results from exposure to cold. The sympathectomized extremity felt subjectively warm throughout the experiment, although objectively it became cold. The patients variously described this sensation as that of the sympathectomized hand or foot "being in an oven," as that of its being "as warm as toast" or as that of "a warm breeze blowing on it [the sympathectomized zone of skin]." In the case of the upper extremity particularly, the patients did not at any time experience an aching or stinging pain in the fingers and hand on the side of operation, even though these parts were objectively as

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1. Hyndman, O. R., and Wolkin, J.: The Autonomic Mechanism of Heat Conservation and Dissipation: II. Effects of Cooling the Body; a Comparison of Peripheral and Central Vasomotor Responses to Cold, Am. Heart J., to be published.

cold as, or colder than, their normal mates when the latter began to pain acutely.

We also pointed out that patients who had had a unilateral cervicodorsal ganglionectomy could tightly clutch a block of ice in the sympathectomized hand much longer than they were able to tolerate it in the normal hand.

One of the patients (E. R.) whom we included in the previous report [1] and who had had a section of the right splanchnic nerves and removal of the first and second lumbar ganglia on the right returned for follow-up examination Nov. 14, 1940, twenty-five months after operation. She stated that whenever her feet are exposed to cold the left, or normal, foot always feels much the colder to her. This foot may ache and sting if sufficiently cold, but these sensations have not occurred in the denervated foot since operation.

PRESENT INVESTIGATION

We were intrigued by these results and have carried the experiments further. Since the publication already referred to, we have studied 4 additional patients after a unilateral ganglionectomy.

CASE 1.—E. P., a man who had had an amputation of the left forearm below the elbow, complained of pain in the stump and fantom hand of long duration. After cervicodorsal ganglionectomy he was still conscious of his fantom hand, but he had no pain. When he was placed in the refrigerator he gave the same testimony concerning the sensation of cold that has already been described. The face and arm on the left (denervated) side felt warm, while the right half of the face and the remainder of the body felt cold. Because of the absence of his left hand, we did not carry out further experiments.

CASE 2.—N. B., a woman of 41 with the gastric crises of tabes, had a bilateral anterior chordotomy at the third thoracic level; at the time this was carried out, with the patient's permission, the second dorsal sympathetic ganglion on the right was removed. She was cooperative, and we were enabled to carry out a number of interesting tests. She is grateful for the complete abolition of the severe and incapacitating gastric crises, which has lasted for one year, up to the time of writing. The tests related to the completeness of sympathectomy which we have carried out are informative in a number of ways, and these data will be considered in a subsequent publication. It will suffice at present to say that all of our tests made it evident that removal of the second dorsal ganglion on the right side constituted a complete sympathectomy on that side down to the cutaneous level of the third dorsal nerve. That is, so far as interruption of central connections is concerned, the result corresponds precisely to that following removal of the inferior cervical and upper two dorsal ganglia and hence supports the contention that no sweat, pilomotor or vasomotor fibers reside in the anterior root of the first thoracic nerve. The thermoregulatory sweating test revealed anhidrosis of the right side of the face and the right upper extremity and down to the cutaneous level of the

third dorsal dermatome on the right. The heat-capillary dilatation tests [2] revealed absence of flushing in the zone of anhidrosis. It is with the refrigerator test, however, that we are concerned at present.

Refrigerator Test.—This test was carried out twice, and any questions asked were casual, and not leading. In fact, the patient volunteered the information that throughout the experiment the face and the upper extremity on the right (sympathectomized) side were much warmer than the corresponding areas on the left. After being in the refrigerator for ten to fifteen minutes in the nude except for a loin cloth, she became cold subjectively except in the sympathectomized and analgesic [3] zones. The fingers and ear on the left began to ache and sting from exposure to cold. The right side of the face, the right ear and the right upper extremity remained subjectively warm, and after an hour the fingers of the right hand still felt warm to her and she never experienced the sting of cold in that hand. She was able to outline the sympathectomized zone on the right side remarkably well on the basis of subjective sensation. It is of interest that when she was taken from the refrigerator into a warm room, she was struck with a severe headache which was localized to the left temple (intact side). She stated that it was much like the pain that she experienced when removing her normal hand from ice water.

Heating Test.—A heating test was carried out in the Burdick inductotherm heat cabinet after the hypodermic administration of atropine sulfate. The method has been described in another report.[2] For the purpose of this experiment both upper extremities remained outside the cabinet and were exposed to room temperature. After one hour and ten minutes the oral temperature rose from 98.6 to 101.3 F. Toward the end of the experiment the left (normal) hand felt subjectively "as if it were on fire" or "as if in hot air." The right hand felt cool and comfortable. Toward the end of this experiment, however, the (sympathectomized) hand was objectively cooler by 2 C. (3.6 F.) than the left.

Ice Water Test.—The patient's hands were immersed to equal depths in a pan of ice water. The right hand (on the side of operation) did not feel nearly so cold to her as the left. She was instructed to keep the hands submerged as long as she could reasonably tolerate the cold. She was compelled to remove the left hand in sixty-eight seconds. The aching pain in this hand was emphasized when it was taken out of the water, and the pain lasted five minutes, being so severe it "made her sick at her stomach." She removed the right (sympathectomized) hand in one

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2. Hyndman, O. R., and Wolkin, J.: The Autonomic Mechanism of Heat Conservation and Dissipation: I. Effects of Heating the Body; Evidence for the Existence of Capillary Dilator Nerves in Anterior Roots, Am. Heart J. **22**:289-304 (Sept.) 1941.

3. The patient stated that she felt no sensation at all in relation to pain or temperature below the chest. The lower extremities felt comfortable, were not especially warm or cold subjectively and were devoid of paresthetic, formicating or painful sensations. When her foot was immersed in hot or ice water, she experienced no altered sensation at all except in relation to touch and pressure. This has consistently been our experience with patients after section of the spinothalamic tract, and the result indicates that whatever may be the mechanism of the influence of the sympathetic nervous system on sensation, it is abolished by section of the spinothalamic tract because of the complete loss of sensibility to pain and temperature.

hundred and forty-eight seconds. This hand ceased aching immediately on removing it from the water and became subjectively warm and comfortable. No difference in color of the hands could be discerned, both having the pink, flushed appearance that is usual to this circumstance. Four normal subjects tried to keep a hand in the ice water as long as the patient was able to keep her right hand immersed, but succeeded in doing so only one-sixth to one-half as long. This test was repeated a number of times, always with essentially the same results.

Hot Water Test.—A pan of water was heated to the limit of extended tolerance. When the patient immersed both hands in the water, the right (sympathectomized) hand felt subjectively cooler. The hands were allowed to remain forty seconds and when removed did not pain. The sympathectomized hand continued to feel cooler to her than the normal hand.

Temperature Discrimination on the Two Sides (Flask Test).—Water, the temperature of which was measured, was placed in two 100 cc. Erlenmeyer flasks, and three experiments were carried out without allowing the patient to know the temperature of each flask.

Experiment 1: The temperatures of the two flasks placed one in each hand were the same. Different temperatures were tried, ranging from 8 to 57 C. (46.4 to 134.6 F.), The results are given in the following tabulation.

Temperature, C.	Response	
	Right (Sympathectomized) Hand	Left (Intact) Hand
8	Warmer	Colder
17	Warmer	Colder
23	Little warmer	Little colder
31	Feels the same to both hands	
38	Feels the same to both hands	
47	Cooler	Quite a bit hotter
57	Cooler	Quite a bit hotter

Experiment 2: An attempt was made to see if there was any difference in ability to discriminate temperature in the two hands. The patient was allowed to compare two flasks with only one hand at a time. The temperatures of the two flasks differed as follows: (*a*) 26 and 37 C.; (*b*) 28 and 33 C., and (*c*) 31 and 33 C. In all instances she discriminated between the temperatures of the two flasks correctly with either hand, and the difference in the temperatures of the flasks felt of about the same magnitude in either hand.

Experiment 3: An attempt was made to ascertain roughly the magnitude of the difference in temperature sensibility when using the two hands simultaneously. Obviously, as can be seen from the preceding tabulation, this factor differs for different temperatures. That is, cold objects felt warmer to the hand on the side of operation and hot objects felt cooler. When the object was at a temperature of about 31 to 38 C. it felt the same to both hands. However, when low temperatures were used it was found that to the sympathectomized hand a flask at 12 C. felt of the same temperature as a flask at 21 C. did to the left (intact) hand. Hence the difference in temperature appreciation of the two hands at this temperature level was roughly about 9 C.

Case 3.—L. C. had had a bilateral section of the anterior and posterior roots from the first to the fifth thoracic, inclusive,[4] and a modified bilateral chordotomy [5] twenty months before for essential hypertension. The inferior cervical and first dorsal ganglion on the right were removed ten months before in an attempt to relieve a causalgic type of pain in the right side of the chest and the right shoulder.

Ice Water Test.—Both hands were immersed in ice water. The patient was compelled to remove the left (intact) hand in twenty-eight seconds. The aching and stinging pain was emphasized on removing the hand, and the pain continued for four minutes. She was compelled to remove the right (sympathectomized) hand in eighty seconds. On removing the hand the aching pain ceased quickly, and the hand felt subjectively warm.

Flask Test.—Experiment: Flasks containing water of the same temperature were held in each hand simultaneously. The results are expressed in the following tabulation.

Temperature, C.	Response (Sympathectomized) Right Hand	Response Left (Intact) Hand
8	Cold	Colder
17	Cold	Little colder
23	Warm	Definitely warmer
31	Warm	Warmer
38	Warm	Warmer
47	Hot	Hotter
57	Hot	Definitely hotter

Experiment 2: Two flasks of different temperatures were examined in each hand separately. Three trials were made, with the flasks at 26 and 37, 28 and 33 and 31 and 33 C., respectively.

The patient could distinguish the flasks correctly in either hand but felt that she could more easily tell the difference in the left (intact) hand.

Experiment 3: A flask at 12 C. in the right (sympathectomized) hand felt the same as one of 19 C. in the left hand. Hence, at this temperature level the difference in temperature sensibility on the two sides was of the order of 7 C.

Comment.—The results of the ice water and the flask tests in this case agreed remarkably well with the results in the case of N. B. When the flask test was carried out on N. B., the average temperature of the fingers of one hand did not at the time differ from the average of the other hand by more than 0.5 C. (0.9 F.)

4. This does not constitute sympathectomy of the upper extremities (Hyndman, O. R., and Wolkin, J.: Sweat Mechanism in Man: Study of Distribution of Sweat Fibers from the Sympathetic Ganglia, Spinal Roots, Spinal Cord and Common Carotid Artery, Arch. Neurol. & Psychiat. **45**:446-467 [March] 1941).

5. A cataract knife was inserted toward the center of the cord, beginning just anterior to the dentate ligament. The final section was made about 2 to 2.5 mm. in an anteroposterior direction. This section injures the posterior aspect of the spinothalamic tract and results in loss of sensibility to pain and temperature for varying distances up the lower extremities (Hyndman, O. R., and Van Epps, C.: Possibility of Differential Section of the Spinothalamic Tract: A Clinical and Histologic Study, Arch. Surg. **38**:1036-1053 [June] 1939). This patient sustained loss of sensibility to pain and temperature up to the groin on both sides.

at room temperature (26 C.). At the time the flask test was done on L. C., the sympathectomized hand was 1 C. (1.8 F.) warmer. However, if this difference accounted for the fact that a hot object felt cooler to the warmer hand, then, by the same reasoning, a cold object should have felt colder to the warmer hand, which was not the case.

INTRAVENOUS DRUGS

Investigations on the action of a solution containing 42 Gm. of magnesium sulfate, 16 Gm. of calcium gluconate, 0.9 Gm. of sodium chloride and 1 mg. of copper sulfate in 100 cc. of distilled water [6] have been carried on by Spier, Wright and Saylor [7] and by Kvale, Smith and Allen.[8] With the idea that this solution produces the sensations peculiar to it by acting on vessels, we tested the action of the substance on L. C. An ampule was injected intravenously. The results are shown in the following tabulation:

	Circulation Time, Seconds		
	Arm to Tongue	Arm to Right Hand	Arm to Left Hand
10/23/40	9	19	18
10/24/40	8	24	23

The patient felt no sensation of heat or pain in the perineum or the feet. This fact can be explained no doubt by the chordotomy. The characteristic sensation of heat and pain was felt in the right (sympathectomized) hand but, according to the patient's testimony, was at most only half as intense as that felt in the left hand.

This test was carried out on 2 other patients who had had bilateral sympathectomy of the upper extremities. Both patients experienced the sudden sense of warmth and slight pain when the drug reached the tongue and hands. Therefore the sensation provoked by the solution is not abolished by sympathectomy.

COMMENT

Little has been published concerning the possibility of altered sensation following sympathectomy. Those who have written feel they have demonstrated hyperesthesia in the sympathectomized zone. This is contrary to our results. Dusser de Barenne [9] reported the presence of

6. The solution, known commercially as macasol, is obtainable from the Nepera Chemical Company, Inc., Yonkers, N. Y. When injected intravenously it produces a sensation of warmth throughout the body but, apart from this general feeling, causes a flash of heat to be experienced successively in the throat, the perineum, the hands and the feet. The time elapsing between injection of the solution and detection of the reaction is known as the circulation time. A pamphlet giving instructions for injection may be obtained from the manufacturers.

7. Spier, L. E.; Wright, I. S., and Saylor, L.: A New Method for Determining the Circulation Time Throughout the Vascular System, Am. Heart J. **12**:511-520 (Nov.) 1936.

8. Kvale, W. F.; Smith, L. A., and Allen, F. V.: Speed of Blood Flow in the Arteries and in the Veins of Man, Arch. Surg. **40**:344-351 (Feb.) 1940.

9. Dusser de Barenne, J. G.: L'influence du système nerveux autonome sur la sensibilité de la peau, J. de psychol. **28**:177-182, 1931.

hyperesthesia in cats after ganglionectomy. Foerster, Altenburger and Kroll [10] reported that sensory excitability in man was augmented after sympathectomy and that the chronaxia of touch and pain points was diminished. Pette,[11] in a discussion of the presence of paresthesias in sympathectomized zones, stated that sensations were different from those of normally innervated zones. Tournay and Claude Bernard, cited by Dusser de Barenne,[9] made similar observations. Tournay found sensibility of the skin of the dog's leg increased after lumbar ganglionectomy. Claude Bernard found increased sensibility on the corresponding side of the face after superior cervical ganglionectomy in rabbits and cats.

On the contrary, Brown and Adson [12] found tenderness of the sciatic nerve in only 2 of 36 cases after lumbar ganglionectomy. Hyperesthesia was not complained of or elicited. They reported that some hyperesthesia and soreness of muscles and nerve trunks were present in all cases after thoracic ganglionectomy. The disturbance disappears after ten days to five weeks and may be minimized by careful handling of the peripheral nerves. They stated that trauma to the first and second thoracic nerves is probably the major factor in causing the pain.

We have encountered annoying pain in the upper extremity after cervicodorsal ganglionectomy, and such experience is undoubtedly universal. We have concluded that this is purely a somatic disorder following some degree of trauma to the somatic nerves, particularly those of the brachial plexus during the removal of the inferior cervical ganglion. Recently, in a case of Raynaud's disease, we removed the inferior cervical and the upper two dorsal ganglia on the left side, and on the right we cut all rami of the second and third dorsal ganglia and the chain elbow the third dorsal ganglion. The inferior cervical and first dorsal ganglia on the right were not molested. The thermoregulatory sweating tests, as well as other tests, proved that both upper extremities were equally and completely sympathectomized so far as central connections were concerned. For six weeks after operation the left arm and hand were tender and painful, the condition closely simulating peripheral neuritis. The right upper extremity was comfortable and in no way troublesome.

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10. Foerster, O.; Altenburger, H., and Kroll, F. W.: Ueber die Beziehungen des vegetativen Nervensystems zur Sensibilität, Ztschr. f. d. ges. Neurol. u. Psychiat. **121**:139-185, 1929.

11. Pette, H.: Das Problem der wechselseitigen Beziehungen zwischen Sympathicus und Sensibilität, Deutsche Ztschr. f. Nervenh. **100**:143-164, 1927.

12. Brown, G. E., and Adson, A. W.: Physiologic Effects of Thoracic and of Lumbar Sympathetic Ganglionectomy or Section of the Trunk, Arch. Neurol. & Psychiat. **22**:322-357 (Aug.) 1929.

Fulton [13] reported a case in which the rami of the second, third and fourth lumbar ganglia were interrupted and the lumbar portion of the chain was severed. The patient stated a year later that the corresponding leg was "tingly." The skin was hyperesthetic as compared with the left, and compression by a blood pressure cuff was more painful. Fulton expressed the belief that the vasomotor effects attending the sympathectomy were in some way responsible for the condition. Livingston [14] did not observe hyperesthesia in his patients after ganglionectomy but stated that Donal Sheehan, in a personal communication, reported that he had demonstrated a slightly lowered threshold for sensation to touch in 15 patients subjected to sympathectomy. Sheehan expressed the belief that the lowered threshold was attributable to increased vascularity around the somatic sensory receptors, but in none of his cases was there a sufficient change in sensation to be termed hyperesthesia.

We quote Leriche [15] as follows (page 47):

> In 1851, Claude Bernard showed that excision of the superior cervical ganglion in the rabbit led to an increase of the sensibility of the corresponding side of the face—a phenomenon the reverse of which I have described.
>
> One thing is clear: by suspending the activity of the sympathetic it is possible to check spontaneous pain affecting the distribution of a cerebro-spinal nerve.
>
> And so, we cannot any longer picture pain to ourselves as a simple phenomenon, to be explained by the passage, along a conductor, of an impulse proceeding from one point to another. We are dealing here with something much more subtle and complex, and from the physiological point of view, concerned with other influences than we had imagined. The matter is much more varied than would be consistent with the far too graphic sketch-plan we have hitherto accepted so complacently.

Our results involve a comparison of the sympathectomized side with the normal side and indicate a diminished sensibility to temperature on the sympathectomized side as compared with the normal side. So far as pain is concerned, it is only the aching, stinging pain from exposure to cold that is diminished. We have not been able by ordinary methods of examination to elicit any changes in the sensibility to touch and pinprick after lumbar ganglionectomy or after sympathectomy of the upper extremities if the latter are comfortable and without pain when tested. Nor have we been able to elicit any alteration in the ability to discriminate changes in temperature over the sympathectomized zone

13. Fulton, J. F.: Vasomotor and Reflex Sequelae of Unilateral Cervical and Lumbar Ramisectomy in a Case of Raynaud's Disease, with Observations on Tonus, Ann. Surg. **88**:827-841, 1928.

14. Livingston, W. K.: The Clinical Aspects of Visceral Neurology with Special Reference to the Surgery of the Sympathetic Nervous System, Springfield, Ill., Charles C. Thomas, Publisher, 1935, p. 179.

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itself. We stated in a previous publication [1] that our findings in the refrigerator test may indicate the existence of afferent sympathetic fibers to the skin or the vessels of the skin and that our results might be due to the interruption of such afferent fibers. There is at least one other explanation, namely, that the efferent sympathetic nerves in some way influence the threshold of somatic sensory endings. The question concerning which, if not both, of these two theories is correct, is an old and unsettled one. There is a great mass of data related to each side of this question, and we have procured some evidence of our own that would indicate the existence of pain-bearing afferent sympathetic fibers from the skin and peripheral vessels. The review and presentation of this evidence will be reserved for a separate publication. However, we shall report the following 2 cases which indicate the possibility of the existence of sensory sympathetic fibers to the lower extremities.

CASE 1.—L. M., a white man of 30, presented long-standing flaccid paralysis of both lower extremities as a result of a spinal fracture at the second lumbar vertebra. There were atrophy of the thighs and legs and absence of the knee jerk, ankle jerk and plantar reflex. There was complete anesthesia to all tests for exteroceptive and proprioceptive sensation up to the region of the midthigh on both sides. The thermoregulatory sweating test revealed that the sympathetic supply to the lower extremities was intact. The patient stated that when lying quiet he could feel pulsations in his feet that were synchronous with his heart rate. When his body became chilled his legs felt subjectively warm, and when his body was warm his legs felt subjectively cool. Rubbing his abdomen made his feet "tingle," as a normal extremity does when "it goes to sleep." When his feet were squeezed and then released he felt a stinging sensation appear and disappear slowly. When a blood pressure cuff was attached to the lower portion of the thigh just above the knee and was inflated sufficiently to collapse the arteries he experienced marked "tingling" in the foot, as if the latter were "asleep."

CASE 2.—H. T., a white man of 28, presented complete paralysis of both lower extremities of seventeen months' duration as a result of a fracture of the second lumbar vertebra. There were loss of voluntary function of the bowels and bladder and complete anesthesia to exteroceptive and proprioceptive stimuli up to the groins. There was also anesthesia of the saddle area and of the genitals. The knee and ankle jerks and the plantar reflex were absent. A thermoregulatory sweating test revealed the sympathetic supply to the lower extremities to be intact. The patient experienced no sensation when a strong electric current (faradic) was applied to the skin of the lower extremities. Twenty seconds after the foot was immersed in ice water he experienced a "tingling" and "pins and needles" sensation and aching in the foot. These sensations were emphasized with every pulse beat. Pressure applied to the foot after it was removed from ice water emphasized the paresthetic sensations. The latter endured for about seven minutes after removal of the foot from the ice water. This experiment was repeated three times, with the same results.

Such results as these indicate that a certain type of sensation may be mediated by the sympathetic fibers, and in this case, in which the somatic nerves have been interrupted, one would be compelled to postulate

activity of afferent sympathetic fibers or antidromic activity of efferent sympathetic fibers. The results in these 2 cases might appear to be inconsistent with the statement made previously concerning the effects of section of the spinothalamic tracts. For example, why did not the patients after section of the spinothalamic tracts experience the same formicating sensations as did the 2 patients with anesthetic lower extremities? It may be that the preservation of touch and pressure sensibilities in the former obscures these vague sensations that are appreciated by the latter.

We should like to call attention to a sensation that is undoubtedly of common experience—the "chill that goes up one's spine" as a transitory emotional reaction to certain impressive situations. For example, a short time ago one of us (O. H.) was listening to a symphony concert on the radio. When a particularly beautiful and impressive passage was being played a wave of formicating sensation spread over his skin. It seemed to begin in the upper extremities and quickly spread to the head and down to the toes. The phenomenon was particularly marked on the scalp and felt much like the sensation provoked when standing close to high tension electric wires. There were a mild pilomotor reaction (goose pimples) over the upper extremities and slight watering of the eyes. The whole phenomenon lasted only a second or two. The reaction is undoubtedly provoked through the agency of the efferent sympathetic nerves and is initiated in the cortex. Whether the "crawling" sensation is mediated by afferent sympathetic or by afferent somatic sensory nerves is open to conjecture, but in any case the phenomenon is an example of spontaneous sensation initiated undoubtedly through the agency of the sympathetic system.

Good example

SUMMARY

Evidence is presented to show that a sympathectomy has a pronounced influence on the interpretation of high and low temperatures when the sympathectomized part is compared simultaneously with a normally innervated part. A cold object feels warmer and a hot object feels cooler to the sympathectomized hand than to its normal mate. When a sympathectomized zone of the skin is tested alone no alteration can be elicited in the sensibility to or the discrimination of touch, pain and temperature as compared with these faculties on the normal side.

A sympathectomy diminishes, and almost abolishes, the aching and stinging pain in the hand and foot that results from exposure to severe cold.

We believe that our results have greater significance than merely that related to a change in cutaneous temperature occasioned by sympathectomy.

No attempt is made to prove whether such changes are contingent on the interruption of sympathetic afferent or sympathetic efferent fibers. However, 2 cases are presented in which the lower extremities were supplied by sympathetic fibers but were devoid of somatic innervation. Sensation could be evoked by appropriate stimuli.

CONCLUSION

A sympathectomy (1) alters the interpretation of temperature when a sympathectomized area is compared simultaneously with a normally innervated part and (2) greatly diminishes the aching and stinging pain of the hands and feet that results from exposure to severe cold.

REGULATION OF THE TREATMENT OF EPILEPSY BY SYNCHRONIZED RECORDING OF RESPIRATION AND BRAIN WAVES

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The technic of Cobb, Sargant and Schwab [1] in recording the synchronous respiration and electroencephalographic activity of epileptic patients at once suggested the possibility of using this method in controlling the treatment of such patients. In this paper the clinical application of the technic to the therapeutic management of 59 patients with epilepsy is described.

MATERIAL

The patients were all from the Massachusetts General Hospital and from both clinic and private wards. Only those were selected who would submit to several examinations and the necessary therapeutic supervision which this investigation entailed. They comprised 31 patients with minor seizures (petit mal) and 28 patients with convulsions (grand mal). Their ages varied from 5 to 46 years. In addition to this group, 15 normal control subjects were observed in order to insure accurate estimation of the limits of the normal variations with this technic.

A number of epileptic patients with surgically approachable, focal lesions were studied by this method before and after operation. A miscellaneous group of 15 patients with headache, neuroses and other nonepileptic complaints were also examined. The total number of examinations made by this method, including those of 15 controls, was 160. The average number of examinations for the therapeutically controlled group was 3; a number of patients had 7 tests and some only 2.

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* Traveling fellow, the Rockefeller Foundation.

This investigation was aided by a grant from the George Harrington Trust.

Read before the American Psychiatric Association (Section on Convulsive Disorders), Richmond, Va., May 5, 1941.

1. Cobb, S.; Sargant, W. W., and Schwab, R. S.: Simultaneous Respiratory and Electroencephalographic Recording in Cases of Petit Mal, Arch. Neurol. & Psychiat. **42**:1189-1191 (Dec.) 1939.

TECHNIC OF EXAMINATION

A standardized placement of four solder electrodes, each 5 to 10 mm. in diameter, on four quadrants of the head was employed, as shown in the diagram (fig. 1). The first channel took the potentials from the right fronto-occipital leads, the second from the two occipital leads and the third from the left occipitofrontal leads. In addition, a neutral lead from the mastoid process ran to the ground terminal of the apparatus. The recording was thus always by bipolar leads linked together in the manner originally described by Adrian, and later used by Gray Walter.

The gain on each amplifier channel was set so that 100 microvolts from the calibrator caused a 10 mm. excursion of the oscillograph pen. This calibration was maintained at all times, even during seizures, in spite of the blocking of the vacuum tube that sometimes occurred. The speed of the paper was always 3 cm. per second, and high frequency filters kept muscle artefacts at a minimum.

The respiratory records were obtained from the modified standard Benedict-Roth basal metabolism apparatus described in a previous communication.[2]

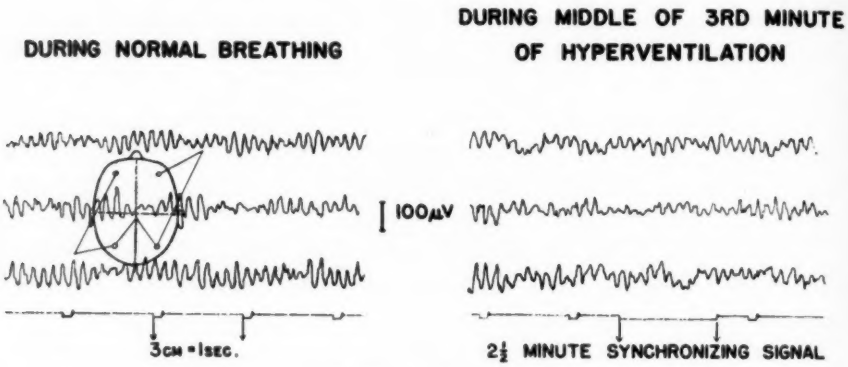

Fig. 1.—Effect of hyperventilation on the encephalogram of a normal control. The standard electrode placements used in this investigation are indicated in the diagram. No significant change is visible during hyperventilation. Note the synchronizing signal in the middle of the timing line.

The patients were all examined while comfortably recumbent, with the head on a pillow. The room was darkened, quiet and air conditioned. An observer always sat by the patient to insure his cooperation and to control the synchronizing signals. There was always an operator in addition who supervised the electroencephalographic apparatus in another room.

The first part of the investigation of each patient included a careful history and the usual neurologic studies. The purpose of the test was carefully explained to each person, so that the element of surprise and anxiety was reduced to a minimum.

The first step in the handling of each patient was to withdraw all forms of anticonvulsant medication for three to four days so that a reliable base line could be obtained. During this period, usually toward the end, an ordinary electro-

2. Sargant, W. W.; Schwab, R. S., and Cobb, S.: Simultaneous Respiratory and Electroencephalographic Recording in Cases of Petit Mal, to be published.

encephalographic examination was made. In this examination a search for focal abnormalities took place. In addition, the patient was introduced to the rather novel atmosphere of brain wave recording and was assured of its painlessness and the comparative simplicity of the test.

When this preliminary introduction was over, the first test with the spirometer was carried out. In this examination time was allowed for relaxation and adjustment to the mouth piece of the basal metabolism apparatus before actual recording took place.

The patient was carefully instructed as to the procedure. He was to breathe quietly and naturally for a few minutes to obtain the first part of the run. Then, at a sign from the attending physician, he began to hyperventilate evenly and deeply in a manner previously demonstrated to him (twenty to thirty respirations a minute, as deep as possible). He continued this overbreathing for exactly three minutes. At the second sign from the observer he resumed quiet, natural breathing for two minutes, until the test was completed.

Each half-minute during the entire test the observer signaled with a key the exact point at which the respiration-recording pen crossed the time line. This was recorded on the electroencephalograph paper, as illustrated in figure 1. The beginning and the end of the actual respiration record were also indicated by the same signal pen as a series of clicks. In addition, the beginning and the end of the period of actual hyperventilation were similarly recorded. All these signal intervals are longer than the instantaneous timing clicks of the telechrone clock, which occurred each second, so that confusion never occurred. Each signal received was properly marked at the time in pencil on the brain wave tape by the person in charge of the machine, so that accurate correlation of the two records was easy.

The time consumed for the synchronized run was six minutes, which was divided as follows: one minute of quiet breathing, three minutes of hyperventilation and, again, two minutes of quiet breathing. When this time had elapsed, the drum on our basal metabolism machine had completed one revolution. Each half-minute of the entire test was recorded, and the period of hyperventilation was differentiated from the period of normal breathing by means of the signal pen.

On our machine the actual respiratory volume was recorded by a second pen attached to a special ventilometer ratchet wheel [3] which had been built into the standard basal metabolism machine.

At the end of the run, before removing the scalp electrodes, the breathing record was inspected for errors arising from leaks in the mouth piece or other sources, and the brain wave record was inspected as well to insure the presence and identification of all signals.

After a satisfactory base line had been obtained in this way, the preliminary anticonvulsant medication was prescribed for the patient. The choice for this initial medication was subject to individual preferences and, of course, to the history of the patient. The severity of the epilepsy, the type of the disease and the amount of time the patient may have for regulation played an important part. Phenobarbital, 1½ grains (100 mg.) daily, may well be employed for initial medication, or dilantin sodium (diphenyl sodium hydantoinate), 1½ grains three times a day, may be used instead.

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3. Reichert, P., and Roth, H.: The Ventilograph: An Improved Recording Ventilometer and Its Applications, J. Lab. & Clin. Med. **25**:1091-1096, 1940.

The second examination should be made three or four days after the first medication is prescribed, and subsequent tests should be carried out approximately four to fourteen days apart, after each adjustment in medication is made. Before going into details of this readjustment, the technic of interpreting the first examination should be considered.

CORRELATION AND INTERPRETATION OF RESPIRATION AND BRAIN WAVE RECORDS

Respiration Record.—The spirogram is laid out on a table and each half-minute marked off. The minute respiratory volume is determined for each half-minute in one of two ways:

With No Ventilometer Pen Incorporated into the Machine: The sum of the lengths of all inspiratory lines is measured by means of a cartographer's pencil [4] for

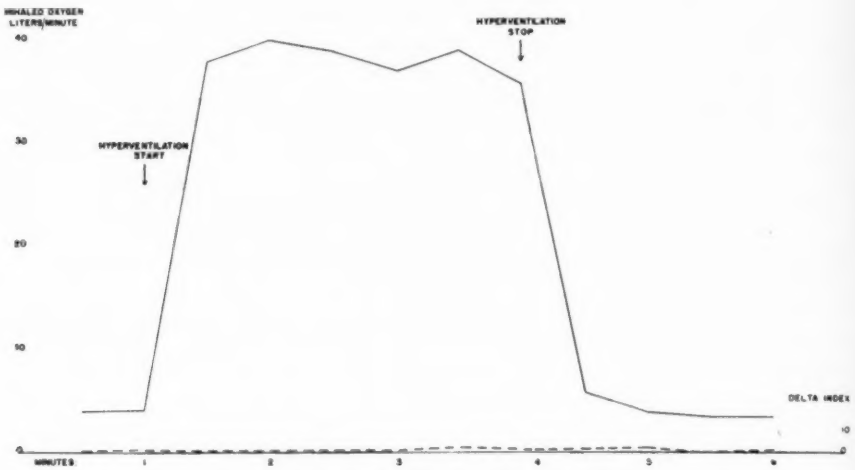

Fig. 2.—Normal control (P. G.) aged 34. In spite of excessive hyperventilation, with a minute respiratory volume of 40 liters, the delta index remains within normal limits.

each half-minute period. Such a device is not essential for this procedure, as a pair of dividers or a centimeter ruler can be used, but it is absolutely necessary for the subsequent determination of the delta index. Therefore, as it makes the determination of the respiratory volume easier, it may also be used for this purpose.

With Ventilometer Pen Built into the Spirometer: The minute respiratory volume for each half-minute is read directly as the height of the line from the horizontal. These readings are then charted on a sheet of millimeter graph paper, so that time in minutes is indicated on the vertical line on the left (fig. 2).

Brain Wave Record.—This is laid out on the table and divided into half-minute sections according to the numbered synchronizing signals. Each half-minute is

4. Made by Keuffel & Esser Co., Switzerland, and obtainable from the B. L. Makepeace Co., 387 Washington Street, Boston, for $6.25.

then measured with the cartographer's pencil according to the method of Hoagland.[5] The half-minute of the record will be exactly 90 cm. long (3 cm. per second), and the "pencil" reading, if no delta waves occur, should be 90. Delta waves are here considered as waves slower than 7 per second.

Since delta index readings are all based on a meter (100 cm.) of brain wave record, a correction factor, $\frac{10}{9}$, must be applied to this value, which represents only 0.9 meter (90 cm.). Subtracting 100 from the number (which is always 100 or above) gives the excess factor of Hoagland, or the delta index.

In the presence of slow, or delta, waves the "pencil" reading will be in "excess" of 90 according to the amount and amplitude of these waves, and when multiplied by $\frac{10}{9}$ gives the accurate half-minute value. We consider 100 to 105 (0 to 5 delta index) as normal. The pathologic records, full of slow waves, give values of 20 to 100, or even 250 in some cases. Further accuracy may be insured by having another person check the reading. We have found that, after some preliminary inaccuracies and difficulties, a high degree of uniformity is soon developed and rechecking the delta index is not necessary, particularly if the same person does it carefully each time.

The delta index for each half-minute is then recorded on the same graph paper, using the ordinate on the right for its value (fig. 2). Combined respiration and delta curves for a normal control are shown in figure 2. It is clear from this record that in spite of excessive overbreathing no change occurred in the delta index. In other words, this subject was able to withstand considerable hyperventilation alkalosis (which indicates the subject's tolerance for this form of convulsant) without development of delta waves. We have examined 15 normal subjects by this method, and all of them showed essentially the same pattern, namely, no, or only a trivial, rise in the delta index with excessive hyperventilation. The index never exceeded 5 even when the respiratory volume was approximately 40 liters per minute (fig. 2). All our normal controls were free of any neurologic disorder and did not have epileptic relatives as far as we could determine. Since Hallowell Davis stated (in a personal communication) that during hyperventilation a low blood sugar causes a rise in the delta index, all our tests were done between one to three hours after a full meal. Students, technicians, physicians and a few cooperative friends were used as normal control subjects.

ILLUSTRATIVE CLINICAL CASES

The cases of 2 patients illustrate the method of controlling the treatment of patients—one having minor seizures, or petit mal, and one convulsions, or grand mal.

CASE 1.—J. C., a girl 19 years of age, was examined for the first time on July 1, 1940, while not receiving any medication. From the moment she entered the room she had a series of slight spells, with short intervals between. She had

5. Hoagland, H.; Cameron, D. E., and Rubin, M. A.: The Electroencephalogram of Schizophrenics During Insulin Hypoglycemia and Recovery, Am. J. Physiol. **120**:559-570, 1937; The Electroencephalogram of Schizophrenics During Insulin Treatment: The "Delta Index" as a Clinical Measure, Am. J. Psychiat. **94**:183-208, 1937.

had epilepsy characterized by this form of seizures for six years. Examination by means of the electroencephalograph and the ventilometer gave the following records:

1. During six minutes of recording she had 16 spells, 2 of them spontaneous (i. e., before overbreathing started) and 6 after overbreathing had been stopped. During each spell she stopped breathing, as can be clearly seen in her spirogram 2 (fig. 3 *A*). The duration of these attacks varied from six to eighteen seconds.

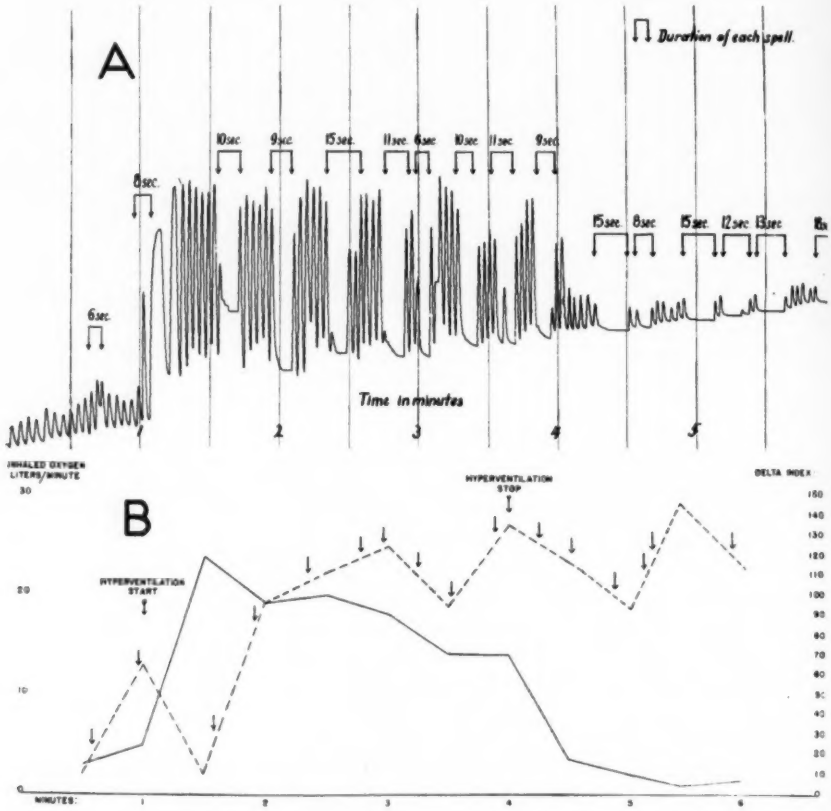

Fig. 3.—In this figure and in figures 4 to 8 are shown the results of tests on J. C., a 19 year old girl with petit mal epilepsy.

Test 1 (July 1, 1940): *A*, spirogram. Sixteen spells occur during six minutes, 8 of which are spontaneous (during quiet breathing). Each spell causes a break in breathing, lasting from six to eighteen seconds. Spells are indicated by arrows.

B, synchronized respiration and brain wave records. Strong slow wave activity caused by the many spells produces a high delta index and interferes with breathing, causing a low minute respiratory volume even during hyperventilation. Spells are indicated by arrows. As in the following figures, the hyperventilation curve is shown by a solid line and the delta index curve by a broken line.

The patient was receiving no treatment during this test.

The amount of oxygen inhaled during these six minutes was measured for each half-minute and then multiplied by 2 to give the minute respiratory volume corresponding to the half-minute period. In figure 3*B* these values are given in liters per minute, as shown by the unbroken line.

Owing to the frequent breaks in breathing, the respiratory curve declines rapidly from 23.6 liters, at the beginning of hyperventilation, to 14.7 liters, at the

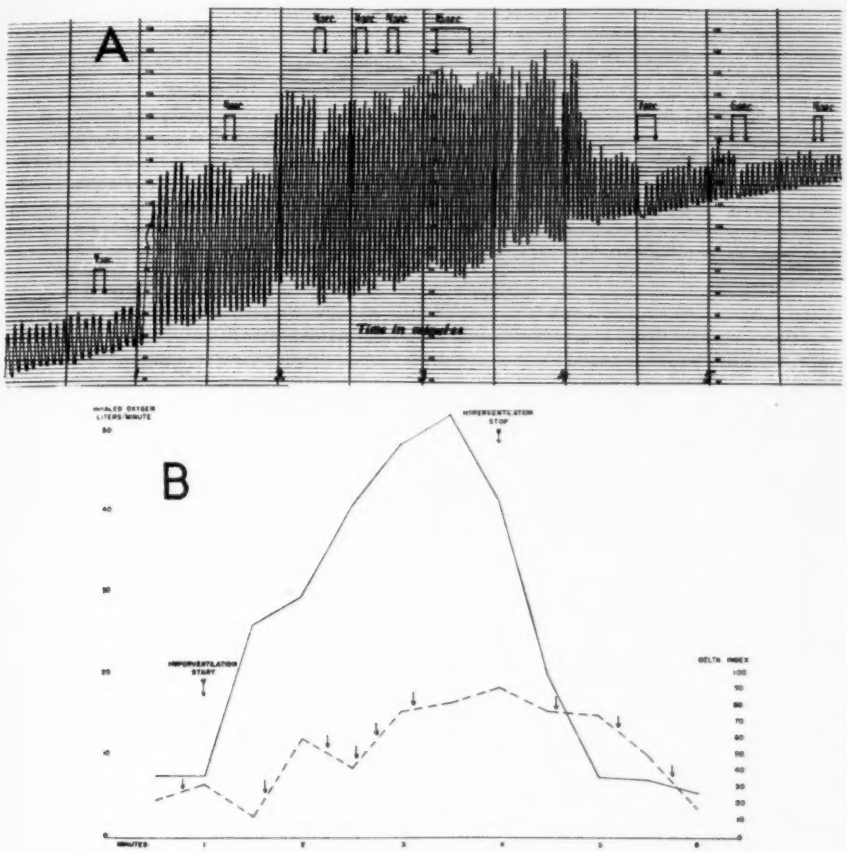

Fig. 4.—Test 2 (July 18, 1940): *A*, spirogram. Breathing stops only in part of the spells. In the other part there is remarkable depression of breathing.

B, less impairment during the spells and faster breathing between them, with increase in the minute respiratory volume. Fewer spells produce a lower delta index.

The patient was receiving 1½ grains of dilantin sodium three times daily.

end of the three minute period of overbreathing, and further decreases to 1.2 liters during the sixth minute.

The delta index shows a quite different picture. It starts at 10, which is higher than normal, rises rapidly with each spell and remains high even during the period of "normal" ventilation following the three minute period of hyperventilation. The arrows show the starting point of each spell.

A recording taken ten days later, when the patient was still without medication, had essentially the same appearance as the one described.

2. After this examination, on July 11, the patient was placed on a regimen of 3 capsules of dilantin (1½ grains [100 mg.] each) daily, and a recording was taken on July 18, 1940, or one week later (fig. 4). During this examination she had 9 spells (1 before and 3 after hyperventilation). The duration of these attacks varied from four to fifteen seconds. This time breathing was much less

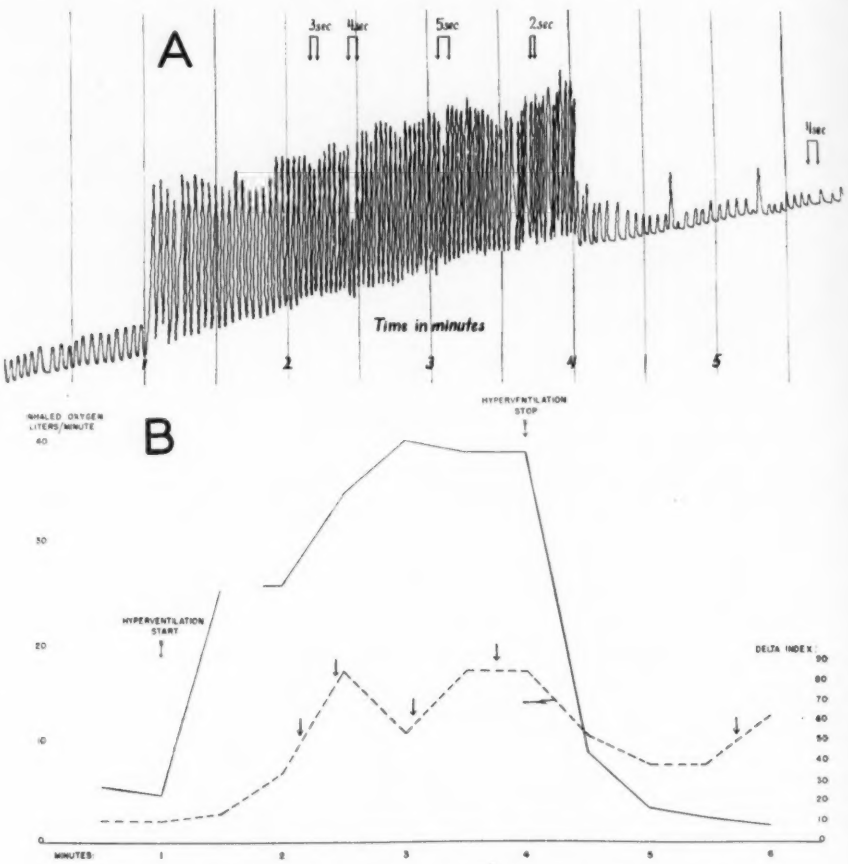

Fig. 5.—Test 3 (Aug. 20, 1940): *A*, spirogram. The spells are fewer than before and of shorter duration, only 1 spell occurring during quiet breathing.

B, good breathing curve. The delta index is lower than in test 2.

The patient was receiving 1½ grains of dilantin sodium five times a day.

affected than during the previous examinations, when she was without medication. During 3 of the spells the period of cessation of respiration was much shorter, and in some the only change was a reduction in the amplitude of the respiratory pattern.

As a result, her breathing curve rose to 52 liters per minute during the three minute period of hyperventilation. Because of the shorter duration of the spells,

the delta index did not rise nearly as high as during the first examination and reached its highest level of 98 at the end of hyperventilation (fig. 4 *B*).

After this test the dose of dilantin sodium was increased to 5 capsules daily.

3. The next examination, on Aug. 20, 1940, showed but 5 spells, of two to five seconds' duration (fig. 5 *A* and *B*). No spells occurred during normal breathing, and the first spell did not occur until the second minute of hyperventilation. The breathing record was about the same as that of July 18.

After this test we added ½ grain (32 mg.) of phenobarbital three times a day to the 5 capsules (1½ grains each) of dilantin sodium.

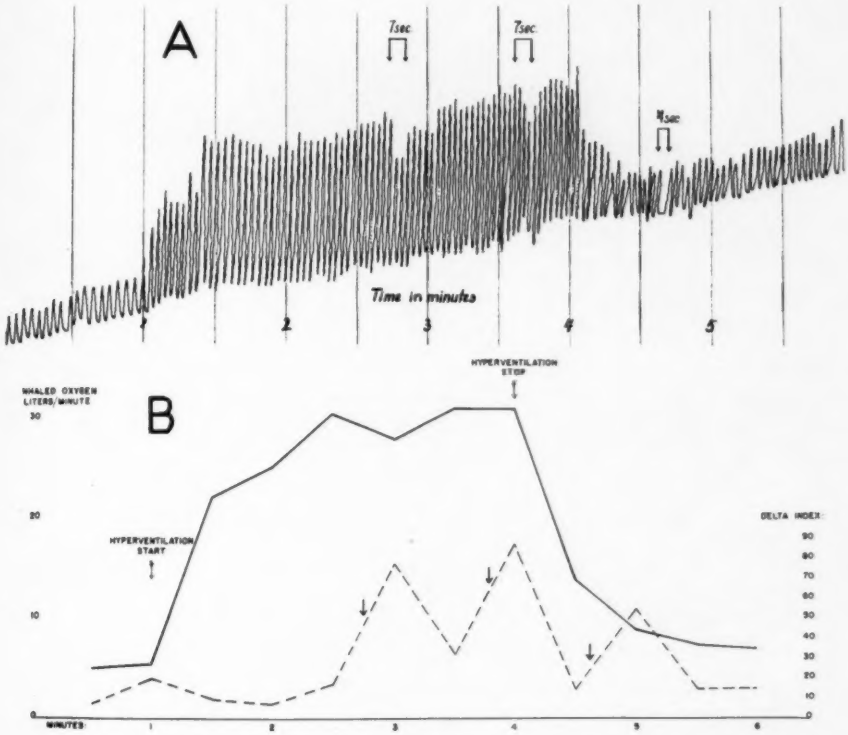

Fig. 6.—Test 4 (Sept. 3, 1940): *A*, spirogram. The first of the three spells occurs during the latter part of hyperventilation (toward the second minute of hyperventilation).

B, curve patterns similar to those in test 3. It can be clearly seen that each spell increases the delta index sharply. Slow wave activity between the spells increases the delta index to 32.

The patient was under treatment with 1½ grains of dilantin sodium five times a day and ½ grain of phenobarbital three times a day.

4. The next test, on September 3, after an interval of two weeks, showed a good breathing curve. Breathing stopped only during the third spell, which was short, while the first two spells had only a depressing effect on respiration (fig. 6 *A*).

The delta index rose during each spell but remained at a low level in the intervals. The longest spell lasted seven seconds (fig. 6*B*).

The patient complained that she felt sleepy and dizzy during the day when she was taking phenobarbital three times daily; so her medication was changed to 5 capsules of dilantin sodium during the day and 1½ grains of phenobarbital in the evening, before retiring.

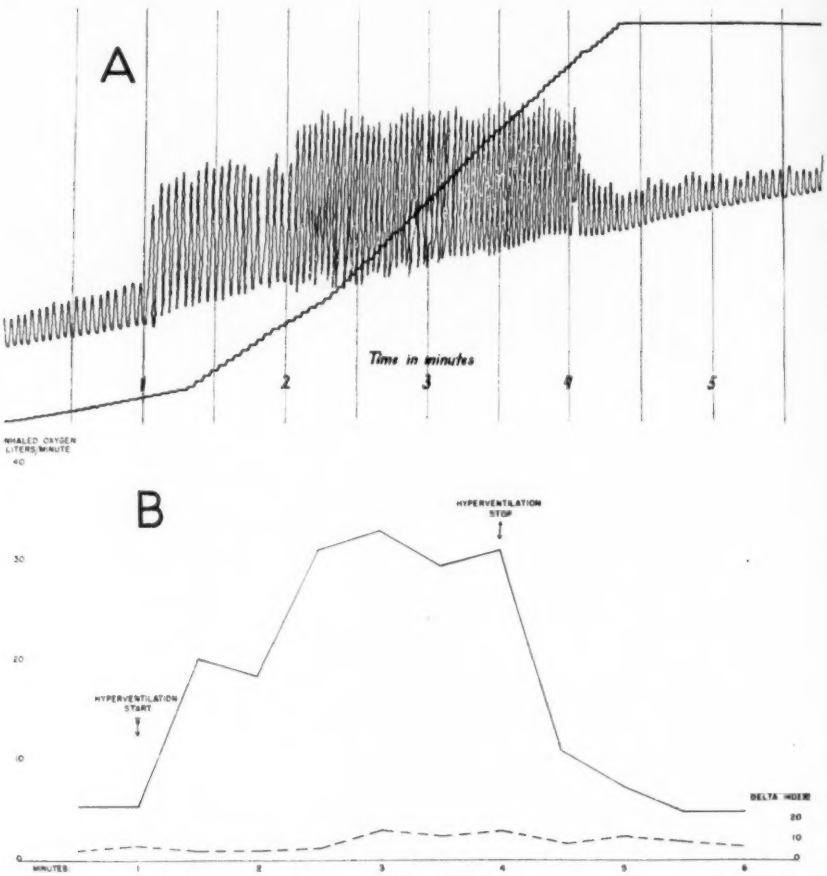

Fig. 7.—Test 5 (Sept. 17, 1940): *A*, spirogram. No spells occur during the entire test. The breathing pattern is normal. The rising line is drawn by a second pen, which records the respiratory volume.

B, normal breathing curve and low delta index, due to little slow wave activity, resulting from the absence of spells.

The patient was under treatment with 1½ grains of dilantin sodium five times a day and 1½ grains of phenobarbital once a day (at bedtime).

5. When she came back two weeks later, on September 17, she told us that from the moment of the last change in her medication no spell had occurred and that she was happy and well.

Her spirogram appeared to be normal (fig. 7*A*). The delta index was only slightly increased during the whole period, while no spells occurred, even during hyperventilation (fig. 7*B*).

This particular case represents a severe type of petit mal not easy to regulate by the usual method. The relative ease with which the

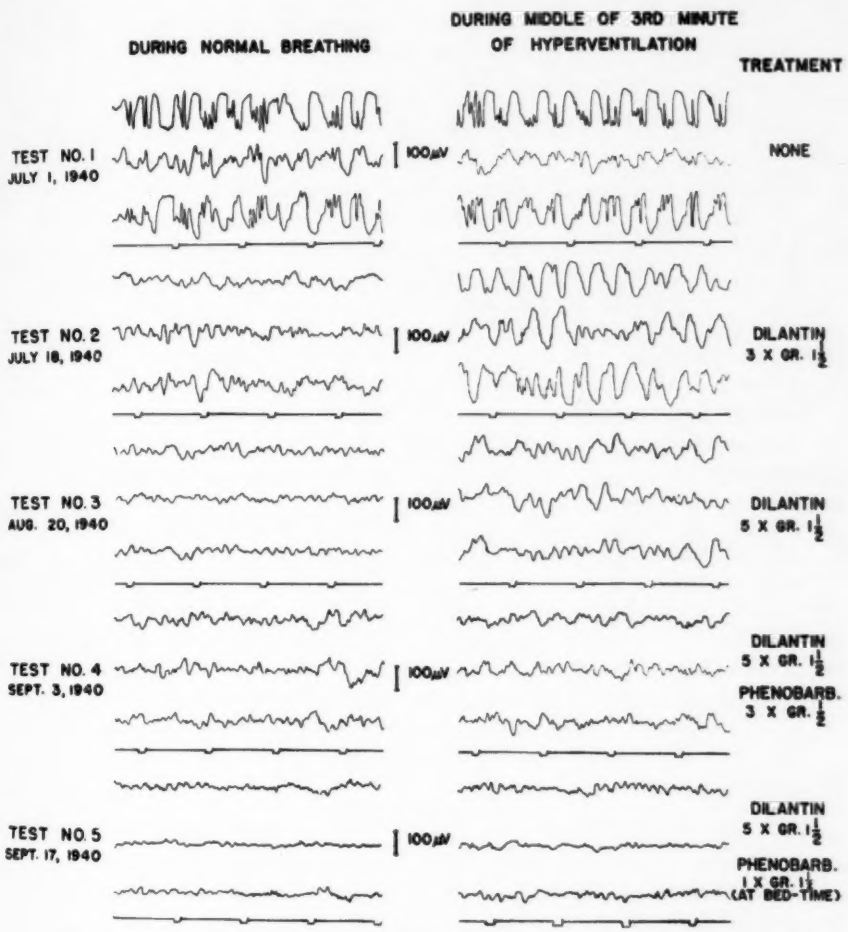

Fig. 8.—The electroencephalogram in the case of J. C. during the various stages of therapeutic management. Records taken during normal breathing are on the left, and those taken during hyperventilation are on the right.

Note the disappearance of spikes after treatment began and the evidence of improvement, as shown in test 5.

attacks were regulated by our method was made possible in part by the breathing–brain wave recording just described. The steady development of resistance to alkalosis with the aid of dilantin and phenobarbital

is clearly seen. Regulation by means of daily spell counts requires a much longer period, and in our experience is not as reliable.

CASE 2.—A. N., a man aged 27, had had convulsions and spells of confusion for four years.

1. The first test was made on June 27, 1940, before the patient had had any medication.

His breathing curve showed a minute respiratory volume of 4.6 liters during quiet breathing, with an increase to 30 liters during overbreathing. This represents an average curve for a person of his age.

His delta index was between 2 and 4 during quiet breathing and rose to 6 during the first minute of hyperventilation, to 17 during the second minute, to 41 during the third minute and to 48 one minute after hyperventilation had been stopped. This rise in the delta index is of a rather mild character and represents in our experience the curve of a patient with rare convulsions.

2. Six days later, on July 3, during which time the patient had been taking 4 capsules (1½ grains each) of dilantin sodium and 3 tablets of phenobarbital (½ grain each), the second test was made.

The delta index remained on a lower level than during the previous test except for a sudden rise after hyperventilation, when a seizure occurred.

After this test medication was increased to 5 capsules of dilantin sodium and 4 tablets of phenobarbital.

3. Nine days later, on July 12, another test was made. The delta index remained on a normal level, a fact which is the more important as his breathing was still more efficient than on the former occasions.

4. When the patient came back two weeks later, on July 25, he told us of a seizure that had occurred in the meantime.

The test showed a slightly higher delta index than on July 12 and brought on an attack after hyperventilation had stopped. His minute respiratory volume rose to only 28 liters. This caused us to increase the amount of phenobarbital by ½ grain daily.

5. Three weeks later, on August 15, during which time the patient was free of convulsions, another test was made, which showed an efficient breathing curve and a delta index that remained under 5, i. e., within normal limits. Since then the patient has been free of convulsions.

The attacks of this patient were difficult to regulate, and the family physician had sent the patient to the hospital. Some of the spells were hard to chart clinically because the patient was unaware of them; our procedure was therefore of great value.

COMMENT

Summary of Cases.—In the following discussion only 17 cases are considered, i. e., those in which three or more tests were made. In the majority of cases the amount of hyperventilation increased under treatment, while normal breathing (as mentioned in another part of this paper) became more regular and quiet than it had been before.

Cobb, Sargant and Schwab [1] found that the number of petit mal seizures produced by hyperventilation is directly related to the amount of oxygen inhaled. We observed that the same principle applies to grand mal epilepsy, although in a somewhat different way. Although convulsions are rarely produced by hyperventilation, the pathologic quality of the brain waves increases during overbreathing, as shown by the elevation of the delta index. This value increases as the minute respiratory volume increases when the patient is not taking drugs. With the patient under treatment a decrease in the delta index despite an increase in hyperventilation may be looked on as indicating considerable improvement.

Of the 17 patients under consideration, 11 responded exceedingly well to anticonvulsant treatment, with the number of seizures declining notably. Their brain wave records showed less abnormal activity, and the delta index decreased as the clinical state improved. Three patients responded moderately well to anticonvulsant treatment; the number and severity of spells diminished only slowly, and, likewise, the improvement of the records took place gradually. One patient with grand mal had no seizures after the first adjustment of drugs (3 tablets, ½ grain each, of phenobarbital daily), while no remarkable change occurred in his electroencephalogram. Even the addition of 3 capsules (1½ grains each) of dilantin sodium daily did not change his record. The addition of 1 capsule of dilantin, however, changed his record completely. The delta index, which up to the last adjustment in medication had remained at 200 during hyperventilation, dropped to 38. During the entire three months of observation the patient had no seizures and was therefore considered clinically improved. One patient showed no clinical response, while his brain wave record became worse with the increased administration of dilantin sodium. Subsequent decrease of dilantin definitely improved the electroencephalogram, while no clinical change could be noted.

Psychologic Effects on Respiration.—In this paper, normal breathing implies that type of respiration common to a certain person when at rest. Most people lying quietly breathe from 4 to 6 liters of air per minute. This value may be regarded as the average normal respiratory volume. Finesinger [6] has shown that many persons produce slower, rounder respiratory patterns with pleasant thoughts. Unpleasant ideas increase the rate and sharpen the respiratory waves. Patients who are upset, worried and anxious may go through various degrees of hyperventilation, depending on many uncontrollable factors, as Cohen and

6. Finesinger, J.: Studies on Respiration in the Psychoneuroses, Arch. Neurol. & Psychiat. **41**:1071-1072 (May) 1939.

Cobb [6a] have described. Therefore, when one states that the normal breathing for a certain subject is, for example, 4.6 liters per minute, one must keep in mind that previously, during the placing of the electrodes or the entry of the subject into the examining room, higher values may have occurred. It is true in our experience that a new, rather tense person may be so apprehensive on his first visit that his "quiet" respiratory volume may be over 12 liters per minute. To eliminate this psychologic hyperventilation as a serious source of error, we prefer to do the respiration–brain wave recording during the patient's second visit to the laboratory. If this is not possible, the examination should follow an ordinary electroencephalographic recording, during which respiration will settle down and the effects of a temporary, psychologically induced alkalosis be allowed to subside.

The results of all clinical tests done during unusual excitement or apprehension are open to criticism. In our series of observations we tried to eliminate this complication whenever possible by repeating the test on a subsequent day. Most patients and their relatives are understanding when the mechanism of the situation is explained to them.

Effect of Drugs on Respiration.—In the previous work, Sargant and associates [2] noted that after taking anticonvulsant drugs some epileptic patients tended to breathe more quietly. There are, of course, several possible explanations for this fact. First, after several experiences with this test the examination is no longer a dreaded adventure, but has become a routine. Apprehension is thereby reduced and psychologic hyperventilation eliminated. Second, the fear of having a seizure is reduced by the knowledge that medicine has been taken that should prevent it. Third, there is some hint that phenobarbital and other anticonvulsant drugs act in a sedative manner, quieting the respiration so that spontaneous overbreathing is less likely.

Mechanical Effects on Respiration.—It is at once obvious that any contrivance to measure the minute respiratory volume has some resistance or friction in its operation. The water spirometer, with adequate-sized rubber tubing (1½ inches [3.8 cm.]) and valves, has an actual resistance to quiet respiration of only 2 to 4 cm. of water. The rubber flutter valves, if not old, are nearly without resistance. The metal bell adequately counterbalanced, with pulley oiled and well attended, offers

6a. Cohen, M. E., and Cobb, S.: Use of Hypnosis in the Study of the Acid Base Balance of the Blood in a Patient with Hysterical Hyperventilation, A. Research Nerv. & Ment. Dis., Proc. (1938) **19**:318-332, 1939. Talbott, J. H.; Cobb, S.; Coombs, F. S.; Cohen, M. E., and Consolazie, W. V.: Acid-Base Balance of the Blood in a Patient with Hysterical Hyperventilation, Arch. Neurol. & Psychiat. **39**:973-987 (May) 1938.

little mass to be overcome. Yet with the ventilation increased to 30 liters per minute during overbreathing these small factors of mechanical resistance increase from 5 to 8 cm. of water and present a tangible problem with which to cope in working with feeble persons or children.

It is possible, through complicated relay valves, to build an electrically operated recording spirometer that theoretically has only a fraction of the resistance of the usual basal metabolism machine. On a trial of the Sanborn waterless, motor-driven basal metabolism machine resistance was found to be half the values just cited. The trial, however, was too short to enable us to make any definite statements regarding its clinical value. Our opinion in this matter may be stated as follows:

Any resistance encountered would reduce the minute respiratory volume and therefore the number of abnormal delta waves in the electroencephalogram. Therefore our curves would not exaggerate the pathologic activity, and would have a constant small negative error. We often found this situation suggested as illustrated by the following case. Hyperventilation without any spirometer measurements (i. e., breathing into the air) produced 3 cycle delta waves and a delta index of 80. When, subsequently, the basal metabolism machine was included in the setup, the delta waves were not slower than 6 per second and the delta index was only 25. This investigation is essentially a comparative study of different determinations on the same subject under various therapeutic states. Therefore this error, when it does occur, is constant. It simply means that the amount of alkalosis induced by voluntary hyperventilation is slightly limited by the frictional resistance of the basal metabolism circuit and that minute respiratory volumes over 40 liters per minute are not usually attainable. Within this limitation great therapeutic differences can be measured, and we see no serious drawback to this barrier.

Some common sources of error in determinations of minute respiratory volume may be mentioned. 1. Old, wet or insufficient soda lime. The delta index remains low during basal metabolic recording and is very high when the patient is breathing into the air. The respiratory rate increases as the procedure continues. 2. A leak in the system. The drum falls without the patient's breathing. 3. Increase in resistance, due to water in the system, a kink in the hose in the flutter valves becoming stuck. Failure of the pen to write, due to a leak in the system, the mouth piece becoming dislodged or the string slipping off the pulley.

Delta Index.—Determination of the delta index is of course subject to some discussion. Hoagland's papers [5] cover most of it. We have found that it represents a relatively accurate method of integrating the

number, height and frequency of abnormal waves. Repeated observations on the same record can be checked with each other. Its errors are those of any measurement. After practice and experience reliable constant values are obtained by the same observer. Artefacts from muscle, eye and head movements are so readily identifiable that they do not bother an experienced worker. Many slow, moderately high voltage waves give values equal to a few slow, very high voltage waves. Seven 6 per second waves may be equal to three 3 per second waves. The delta index does not, therefore, tell one the sort or the degree of abnormality, but indicates the integrated amount of all the abnormal slow waves. This value is what seems to be controlled by the beneficial effects of anticonvulsant drugs.

Duration of Hyperventilation Desirable.—There is some controversy as to how long a person shall hyperventilate in determining the effect of alkalosis on his electroencephalogram. Jasper expressed the opinion that thirty seconds is enough to bring out epileptic waves. Davis suggested continuation up to five minutes, until abnormal waves appeared. They will, of course, occur sooner or later in any subject.

We have found that in our normal control adult group three minutes will not alter the electroencephalographic tracings as expressed by the delta index. On the other hand, several epileptic patients failed to show significant increases of the delta index until the third minute. Patients with rare epileptic convulsions or patients with severe epilepsy who are under treatment may not produce slow waves before the third minute of hyperventilation. Therefore we have chosen this time limit as a desirable test interval for this work.

The amount of hyperventilation obtained depends on two factors: (1) the patient's ability to carry out overbreathing and (2) the freedom from resistance in the circuit. With our machine the extreme value for hyperventilation was 54 liters per minute. We have not equaled the 70 to 80 liters obtained by Brill.[7] Values under 15 liters per minute do not indicate true hyperventilation. We try to reach a volume of 30 liters, which is seven to eight times that for normal breathing. We have not tried to correlate the body weight, surface area or age with the amount of hyperventilation. This might prove interesting and opens possibilities for further work in this field.

One more interesting point may be mentioned. It is obvious that rapid, shallow respiration removes less carbon dioxide than slightly slower, deeper breathing. The effect on the actual minute respiratory value might be the same. We plan later to investigate this point through determination of percentages of carbon dioxide.

7. Brill, N.: Personal communication to the authors.

Standardization of Other Factors.—The position of the patient and, as nearly as possible, the time of day were kept constant. The amplifier gains were always set so that 100 microvolts equaled 1 cm., and the right side of each subject's head was used to determine the delta index. The room was air conditioned and soundproofed to a degree, and efforts were always made to have present the same environment with respect to personnel, etc.

CONCLUSIONS

The method of synchronizing brain wave and respiration recording originally described by Cobb, Sargant and Schwab provides a quantitative check on changes in patients under various therapeutic conditions. Drugs may be more rapidly and accurately adjusted, so that the maximum anticonvulsant effects may be reached. Epileptic patients may be differentiated from normal subjects in that they have a low tolerance to convulsants. In testing patients the simplest and safest means of inducing convulsions is alkalosis. This is readily produced by hyperventilation. It is essential to measure the amount of this overbreathing in liters per minute if any sort of accuracy is to be expected in determining the tolerance of subjects to alkalosis. The basal metabolism machine affords a simple, direct and reliable means and, with the slight modifications mentioned in this and in the previous paper,[1] is practical in its application to this measurement.

The brain wave record should be quantitated if it is to be used to measure the effect of specific amounts of hyperventilation on subjects. Spectral analysis of strips of record by the Grass-Gibbs [8] analyzer is not feasible for most laboratories. Counting the number of abnormal waves gives only part of the answer. Amplitude and frequency must be considered. We have found that the delta index of Hoagland is ideal for this purpose.

The minute respiratory volume and the delta index when plotted together show clearly the effect of changes in breathing on the brain wave pattern. Such charts give an indication of the resistance of the subject to the alkalosis induced by overbreathing. The amount of this resistance can be increased by anticonvulsant drugs. This gives one, therefore, a quantitative method of following the success or failure of drugs or of combinations of drugs and diet on the epilepsy of the patient.

Again, it must be emphasized that such laboratory procedures must not supersede, but must supplement, the usual clinical supervision and handling of patients.

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8. Grass, A. M., and Gibbs, F. A.: A Fourier Transform of the Electroencephalogram, J. Neurophysiol. **6**:521-526, 1938.

SUMMARY

1. The clinical technic of synchronous brain wave and respiration recording is described.

2. Two examples of its use in the regulation of anticonvulsant drug therapy are given.

3. The value and significance of voluntary hyperventilation in all such tests are discussed.

4. The clinical summary of the cases of 59 epileptic patients followed in this manner is included.

INJECTION OF PROCAINE INTO THE BRAIN TO LOCATE SPEECH AREA IN LEFT-HANDED PERSONS

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In cases in which it is necessary for the neurosurgeon to remove portions of the premotor area of the brain, he must first assure himself that in so doing he will not render the patient aphasic. In right-handed persons the center for motor speech always is located in the posterior part of the third left frontal convolution, just in front of the motor center for the face. In congenitally left-handed persons the speech functions usually are located in the corresponding area in the right cerebral hemisphere. The more pronounced the left handedness, the more certain it is that the speech function is located on the right side. Persons who acquire left handedness as a result of the occurrence of right hemiplegia early in life also usually will acquire complete right cerebral dominance, with the speech function located on the right side.

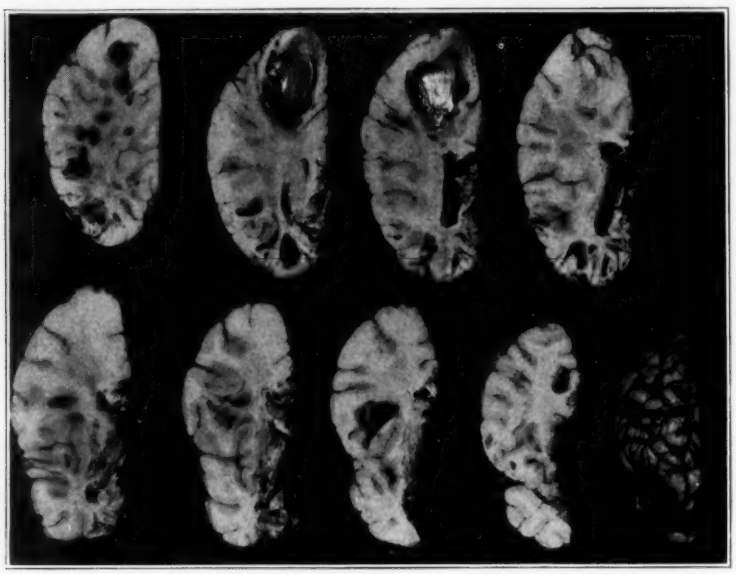
Occasionally, the neurosurgeon is confronted by the problem of a left-handed patient in whom the excision of a portion of the right cerebrum is indicated because of the presence of a tumor or scar. If the lesion already has produced aphasia, one can say that the speech centers are on the right side and the surgeon can govern his actions accordingly. But if, as is frequently the case, the patient has no demonstrable impairment of speech, one cannot from the results of clinical tests state with absolute certainty on which side the function of speech is located. If the excision is planned to include areas which normally serve speech, the surgeon must know beforehand whether or not speech function is served by the right cerebrum. The removal of a tumor at the cost of the patient's speech is scarcely an accomplishment on which to congratulate oneself. The following 2 cases illustrate the method which I employed to determine this point.

REPORT OF CASES

CASE 1.[1]—J. P., a left-handed man aged 35, "had had a progressive left hemiparesis of three months' duration with Jacksonian convulsions which began in the

1. The report of the case quoted here, together with a more complete description of the intellectual status following the operation, has already been published (Karnosh, L. J., and Gardner, W. J.: An Evaluation of the Physical and Mental Capabilities Following Removal of the Right Cerebral Hemisphere, Cleveland Clin. Quart. **8**:94 [April] 1941).

left great toe. The patient presented no symptoms or signs of increased intracranial pressure. The clinical diagnosis was a brain tumor in the right motor area. On Jan. 31, 1938, a right craniotomy was performed. An incision through the cortex in the right premotor area disclosed a subcortical astrocytoma. No attempt was made to remove the tumor. Following this operation, the paralysis of the left arm and leg were almost complete, but there was no weakness of the facial muscles and no aphasia. The patient had been left-handed since birth, he was also left-eyed and the father of the patient was left-handed, indicating that left-handedness was a familial trait, and that the right hemisphere was dominant. The patient was anxious to have the tumor completely removed even though it meant that he would have a permanent left hemiplegia. However, we were reluctant to attempt a radical extirpation of the growth because of the fear that it



"Coronal sections. The lower right is the frontal pole and the upper left, the occipital. The cystic portion of the growth is clearly seen. The site of the procaine injection is represented by the dark cystic area in the middle section, lower row." [1]

would leave him with an aphasia. It was decided therefore to inject novocain [procaine hydrochloride] into the brain in an effort to determine whether the speech centers were on the affected side.

"Nineteen days after the first operation, a trephine opening was made in the right frontotemporal region just in front of the motor center for the face. A hypodermic needle was introduced beneath the cortex of the brain and 27 cc. of ¾ per cent novocaine was injected in various directions. Following this procedure, the patient had a definite paresis of the left angle of the mouth but no aphasia was demonstrable. This we felt proved that the speech center was on the left side of the brain [despite the dominance of the right cerebrum as far as handedness was concerned]. Accordingly, on March 3, 1938 the right cerebral hemisphere was removed with the enclosed tumor. His convalescence following

this procedure was satisfactory, there was no sign of aphasia and he was discharged on the twenty-sixth postoperative day. This patient gets about well with the aid of a cane. His intellectual processes show about the same degree of impairment as has been observed in right-handed persons who have had a similar operation. Physically, however, he is less dexterous due to the fact that he has lost the use of the dominant hand. He has not yet trained himself to write with the right hand. He is still living, three years after operation.

"The specimen weighed 760 grams. . . . Examination showed that the entire hemisphere had been removed except for a thin layer of cortex of the medial aspect of the frontal lobe just in front of and below the anterior genu and the mesial portion of the gyrus hippocampus. The caudate nucleus, all of the putamen and a small portion of the globus pallidus were removed. The thalamus was spared. The tumor consisted of an astrocytomatous cyst in the upper parietal region with a solid portion which extended into both the frontal and the occipital lobes. There were some small cystic areas at the site where the novocain had been injected twelve days previously [figure]. The tumor apparently had been removed entirely."

CASE 2.—R. G., a woman of 27, at the age of 18 months had an illness diagnosed as scarlet fever which was followed by right hemiplegia and convulsions. At the age of 5 years a left frontal craniotomy was performed and a cyst of the brain was said to have been removed. The convulsions continued. The attacks occurred daily and began in the right hand.

The patient's right hand was spastic, atrophied and almost useless. The right leg was mildly spastic. There was no facial asymmetry and no aphasia. The patient, of course, was left handed. As there was no family history of left handedness, it was assumed that the right cerebral hemisphere had acquired dominance because of damage to the left cerebrum at an early age. In an effort to control the frequent seizures, it was decided to attempt to excise the epileptogenic focus.

Operation was performed on Sept. 24, 1940. With the use of local anesthesia, a craniotomy on the left was performed. The dura was thickened and adherent to the arachnoid near the motor center for the face. The arachnoid was thickened and distended with a large quantity of fluid. The cortex everywhere appeared degenerated. With the faradic stimulator the cortex was explored and the motor area located. Ten cubic centimeters of a 1 per cent solution of procaine hydrochloride was injected into the cortex just in front of the motor center for the face. This produced no aphasia, indicating that the speech centers were on the opposite side, as suspected. The injection of procaine also produced no facial weakness, indicating that the motor cortex for the face was nonfunctioning. As a result of this test, the operator felt safe in carrying out a cortical excision. An area of cortex 6 cm. in diameter was removed to a depth of 1.5 cm. by means of sharp dissection. The removed tissue included Broca's area and the lower portion of the motor area.

This patient exhibited no aphasia during her postoperative course. There was marked paresis of the right leg, which was improving nicely at the time of her discharge from the hospital. The convulsions were controlled.

COMMENT

These are the only cases in which I have injected procaine hydrochloride into the brain. To the best of my knowledge no one has produced aphasia by injection of procaine into Broca's area, but that it

would follow such a procedure seems beyond doubt. The amount of procaine used in the first case was probably far in excess of the necessary quantity. When the hemisphere was removed twelve days later, cavities were found at the site of injection. In the case of the patient who was congenitally left handed, the procaine test showed that the speech centers were on the left side. In the case of the patient with acquired left handedness, the test showed that the speech centers were on the right side. Subsequent cortical excisions proved the results of the tests to be correct in each instance.

AMYOTROPHIC LATERAL SCLEROSIS

ORIGIN AND EXTENT OF THE UPPER MOTOR NEURON LESION

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Amyotrophic lateral sclerosis is regarded generally as a disease of the upper and lower motor neurons. The clinicoanatomic description of the disorder, which was first made by Charcot [1] in 1865, was later confirmed by other observers. The gross atrophy of the motor convolutions was observed by Kahler and Pick [2] in 1879. Kojewnikoff [3] was the first to trace the degeneration of the pyramidal fibers from the motor cortex into the internal capsule, peduncles, pons, medulla oblongata and spinal cord. Charcot and Marie,[4] who confirmed Kojewnikoff's [3] observations, also demonstrated the disappearance of the giant pyramidal cells from the motor cortex. These changes were not always constant, and in 1 instance Marie [5] was unable to detect them. Sarbó,[6] Rossi and Roussy,[7] Probst,[8] Campbell [9] and Spiller,[10] in further contributions,

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Read at the Sixty-Seventh Annual Meeting of the American Neurological Association at Atlantic City, N. J., June 9, 1941.

1. Charcot, J. M.: De la sclérose latérale amyotrophique, Progrès méd. **2**: 325, 341, 421 and 452, 1874.

2. Kahler, O.: Ueber die progressiven spinaler Amyotrophien, Ztschr. f. Heilk. **5**:169, 1884. Kahler, O., and Pick, L.: Beiträge zur Pathologie und pathologischer Anatomie des zentralen Nervensystems, Ztschr. f. Nervenh. **5**: 169, 1884.

3. Kojewnikoff: Cas de sclérose latérale amyotrophique. La dégénérescence des faisceaux pyramidaux se propageant à travers tout l'encéphale, Arch. de neurol. **6**:357, 1883.

4. Charcot, J. M., and Marie, P.: Deux nouveaux cas de sclérose latérale amyotrophique suivis d'autopsie, Arch. de neurol. **10**:1, 1885.

5. Marie, P.: Leçons sur les maladies de la moelle, Paris, Masson & Cie, 1892.

6. Sarbó, A.: Beitrag zur Symptomatologie und pathologischen Histologie der amyotrophischen Lateralsklerose, Deutsche Ztschr. f. Nervenh. **13**:337, 1898.

7. Rossi, I., and Roussy, G.: Contribution anatomo-pathologique à l'étude des localisations motrices corticales (trois cas de sclérose latérale amyotrophique), Rev. neurol. **15**:785, 1907.

8. Probst, M.: Zur Kenntnis der amyotrophischen Lateralsklerose, Sitzungsb. d. k. Akad. d. Wissensch. Math.-Naturw. cl. **112**:683, 1903.

(Footnotes continued on next page)

stressed the involvement of area 4; Rossi and Roussy,[7] Probst [8] and Campbell [9] showed that area 6 was also partially implicated in this disease. Marie's [11] original observation that the motor cortex was not involved in 1 instance was completely forgotten by most students of amyotrophic lateral sclerosis. Dercum and Spiller (1899),[12] however, in a case of amyotrophic lateral sclerosis presenting bulbar symptoms, and Spiller,[10] von Czyhlarz and Marburg,[13] Bertrand and van Bogaert [14] and Néri,[15] in other cases of amyotrophic lateral sclerosis, were unable to trace the degeneration higher than the brain stem. Despite these reports, the prevailing opinion is that the pathologic process of the pyramidal pathway begins in the primary motor neurons of the giant pyramidal cells of Betz of area 4, on which are superimposed lesions of the secondary motor neurons of the nuclei of some of the motor cranial nerves (fifth, seventh, ninth, tenth, eleventh and twelfth). The extensive degeneration of the pyramidal tracts in the medulla oblongata and spinal cord is considered by many investigators to be secondary to the involvement of the primary motor neuron in the motor cortex and the secondary motor neuron in the medulla oblongata. The lack of extensive myelin degeneration of the pyramidal tract in the internal capsule and peduncles is explained on the basis that the process is not as marked as in focal lesions. However, as a result of slow and gradual death of the primary nerve cell, the parts most distant from the cell first become affected. It is believed also that if the illness is of considerable standing practically all of the giant pyramidal cells of Betz become ultimately involved. If this is true, no matter how gradual and slow the death of the primary motor neuron, some changes in the pyramidal tract of the internal capsule and peduncles, even if minute, should be detected in all cases of amyotrophic lateral sclerosis by such careful selective staining as is available in the Marchi and sudan III methods. Furthermore, if the disease primarily involves the upper and lower motor neurons, one would expect to find in the spinal cord degeneration only of the respec-

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9. Campbell, A. W.: Histological Studies on the Localization of Cerebral Function, Cambridge, England, University Press, 1905.

10. Spiller, W. G.: Primary Degeneration of the Pyramidal Tracts, Univ. Pennsylvania M. Bull. **18**:390, 1905.

11. Marie, P.: Travaux et mémoires, Paris, Masson & Cie, 1928, vol. 2, p. 285; footnote 5.

12. Dercum, F. X., and Spiller, W. G.: Amyotrophic Lateral Sclerosis Presenting Bulbar Symptoms with Necropsy and Microscopical Examination, J. Nerv. & Ment. Dis. **26**:84, 1899.

13. von Czyhlarz, E., and Marburg, O.: Beiträge zur Histologie und Pathogenese der amyotrophischen Lateralsklerose, Ztschr. f. klin. Med. **43**:59, 1901.

14. Bertrand, I., and van Bogaert, L.: La sclérose latérale amyotrophique, Rev. neurol. **32**:778, 1925.

15. Néri, V.: La sclérose latérale amyotrophique, Rev. neurol. **32**:759. 1925.

tive secondary pathways of these nerve cells. As will be demonstrated, the pyramidal tracts in the internal capsule, the peduncles, the pons and even the medulla oblongata were spared completely in a large number of instances. In many cases there also was involvement of other tracts in the ventrolateral parts of the cord (cerebellar, spinothalamic, etc.). Because of this discrepancy, it was deemed advisable to reinvestigate the problem.

METHOD OF PROCEDURE

Sections from the motor and premotor regions, the internal capsule, the peduncles, the pons, the medulla oblongata and the spinal cord in 42 cases of amyotrophic lateral sclerosis were studied by the Spielmeyer, Bielschowsky, sudan III, Marchi, Holzer and cresyl violet methods. Some of these were embedded in pyroxylin and stained for myelin sheaths and with cresyl violet, while others were frozen and stained by the aforementioned methods. In 5 instances only the spinal cord was obtained at autopsy.

ANALYSIS OF MATERIAL

The cases under investigation were classified in accordance with the highest level at which the degeneration of the pyramidal tract was noted.

1. Cases with involvement of the motor and premotor regions and extension of the process into the pyramidal pathways of the internal capsule, peduncles, brain stem and spinal cord..... 12
2. Cases without cortical involvement in which the process was traced from the peduncles down..... 2
3. Cases without cortical involvement in which the process extended from the pons down..... 7
4. Cases without cortical involvement in which the process involved the medulla oblongata and the spinal cord..... 12
5. Cases without cortical involvement in which the process originated in the spinal cord..... 4
6. Cases in which only the spinal cord was obtained..... 5

Total.....42

Cases of Amyotrophic Lateral Sclerosis with Involvement of the Motor and Premotor Regions and Extension of the Process into the Pyramidal Pathways of the Internal Capsule, Peduncles, Pons, Medulla Oblongata and Spinal Cord (12 cases).—Several interesting features were noted in these cases. The motor and premotor cortex were not equally involved in all instances. The pathologic process was extensive in some and less so in others. In most instances some of the giant pyramidal cells were spared. In some cases the arm area was more involved than the leg area, and conversely. The pathologic process was extensive in 5 of the 12 cases. It consisted of slight distortion of the cytoarchitectural layers (fig. 1 *A* and *B*), small areas of devastation and

severe disease, especially of the giant pyramidal cells of Betz; the medium and small pyramidal nerve cells were less, or not at all, affected. The diseased nerve cells showed a variable picture—chromatolysis with displacement of the nucleus to the periphery, as seen in retrograde degeneration, severe cell changes of Nissl, shadow-like appearance, complete dropping out, incrustations, pyknosis, ischemia, neuronophagia, satellitosis and pigment atrophy. In the Marchi and sudan III preparations there was deposition of fat in the nerve cells, in the perivascular spaces and in the white matter of the centrum ovale; however,

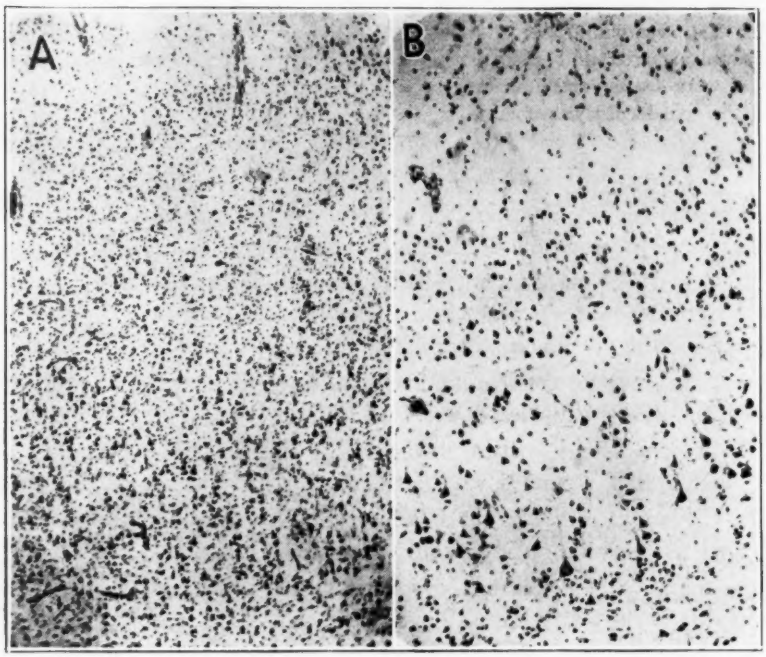

Fig. 1.—(*A*) Distortion in the arrangement of the cytoarchitectural layers, with some dropping out of nerve cells from the motor cortex. Cresyl violet; × 48.

(*B*) Rarefaction and dropping out of nerve cells, especially the giant pyramidal cells of Betz. Cresyl violet; × 40.

the interradiary and tangential fiber systems were spared in most instances. Swollen and occasional fragmented single myelin sheaths and axis-cylinders were detected in the centrum ovale with the Marchi and Bielschowsky stains.

In the 7 other cases the pathologic process was less extensive. There were many normal giant pyramidal cells in the motor and premotor cortex. The diseased cells showed pathologic changes somewhat similar to those in the 5 cases of severe involvement. With the Marchi,

sudan III and Bielschowsky methods broken-down myelin sheaths and axis-cylinders were present in the centrum ovale, but to a less extent than in the first 5 cases.

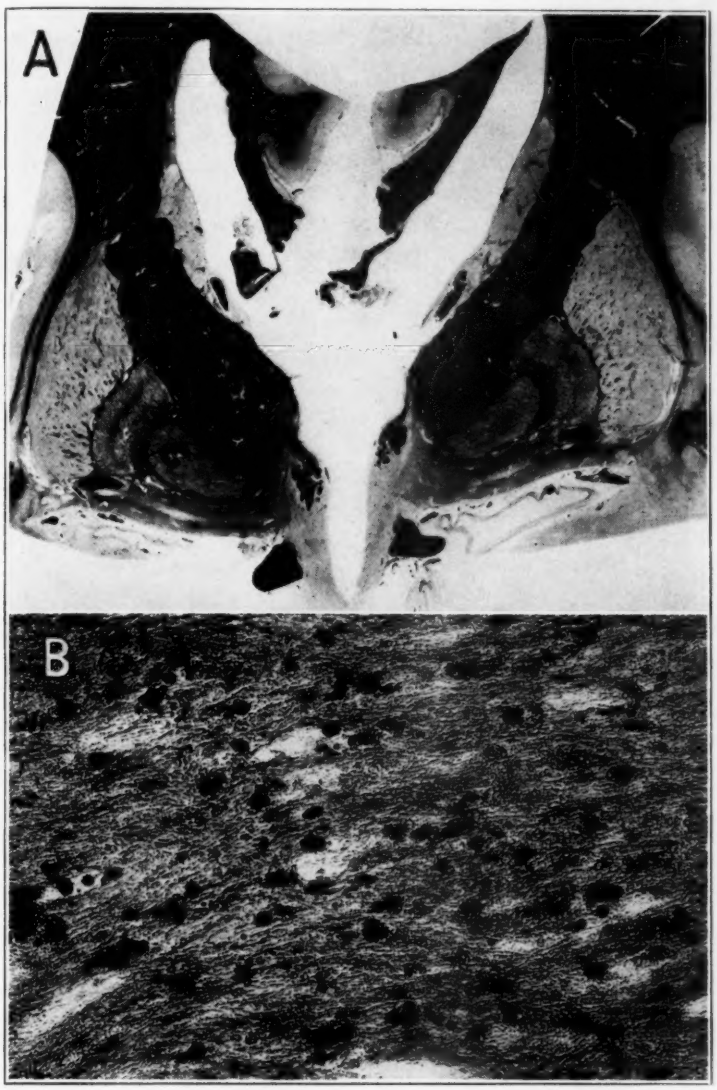

Fig. 2.—Case with cortical involvement. (*A*) The pyramidal pathways of the internal capsule appear intact with low magnification. Myelin sheath stain.

(*B*) Section of the internal capsule in which there was moderate cortical involvement. Although no demyelination could be detected in the myelin sheath preparation (*A*), fat droplets were elicited with the Marchi and sudan III methods. Sudan III stain; × 90.

The pyramidal tracts in the internal capsule appeared intact with a low power lens (fig. 2 *A*), but with the Spielmeyer method the peduncles in 3 of the 5 cases of severe disorder were pale and demyelinated

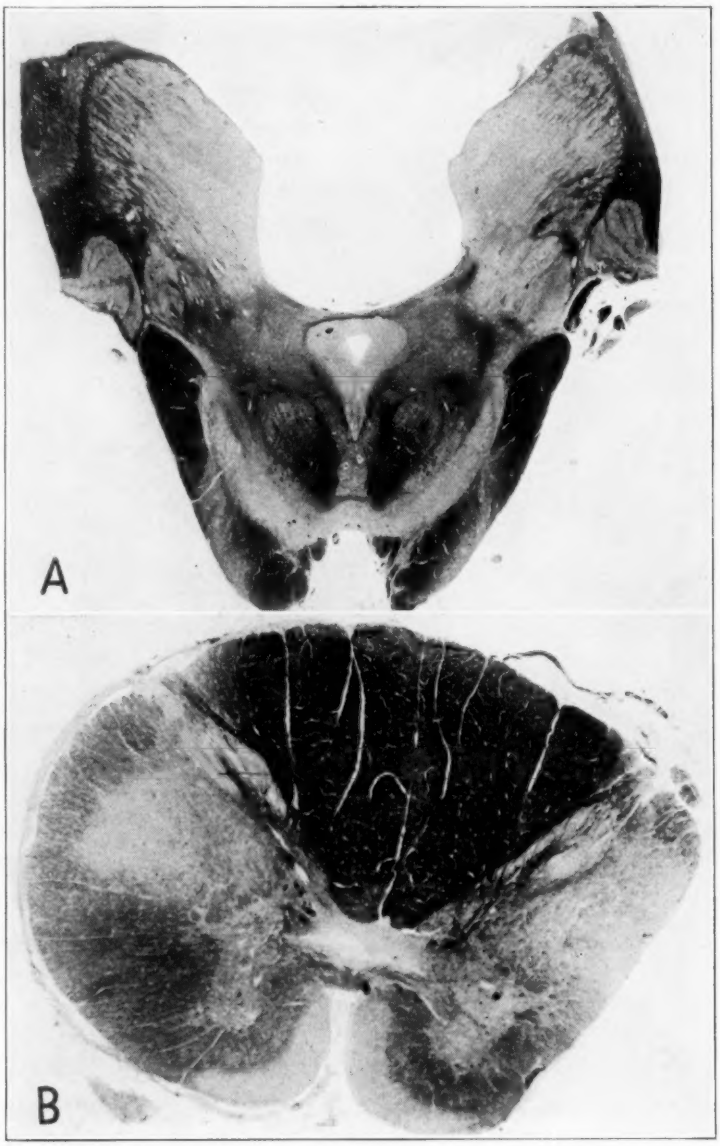

Fig. 3.—(*A*) Case with cortical involvement and demyelination of the pyramidal pathways in the cerebral peduncles. (*B*) Case with cortical involvement disclosing extensive involvement of the pyramidal pathways. Notice that other ventrolateral tracts were also affected. Myelin sheath stain.

(fig. 3 *A*). The degeneration in the internal capsule appeared more severe in the Marchi and sudan III preparations (fig. 2 *B*). It is to be emphasized, however, that even in the cases of severe disturbance some fibers (myelin sheaths and axis-cylinders) were spared. The marked demyelination of the pyramidal tracts could in most instances be observed only below the pons, and it was most extensive in the spinal cord (fig. 3 *B*).

In the 7 cases of less severe involvement the demyelination of the pyramidal tracts in the internal capsule and peduncles could hardly be detected with the myelin sheath and Spielmeyer methods. With a high power lens, however, disintegrated myelin fibers in the form of fat droplets were occasionally noted. This could be seen more easily in the Marchi and sudan III preparations. In the Spielmeyer preparations, however, the demyelination in most instances could easily be seen below the pons microscopically, and in 2 instances it could be observed in the pons with the naked eye.

Other ventrolateral tracts, such as the cerebellar and the spinothalamic, were seen to be partially involved in the myelin sheath and Spielmeyer preparations (fig. 3 *B*) but were best observed in the Marchi and sudan III preparations in 6 of the 12 cases; 3 of these belonged to the group of severe and 3 to the group of less severe involvement. The direct pyramidal tracts were extensively affected in all but 1 of the cases of severe disease, in which they were only slightly involved.

Some observers have expressed the belief that the duration of the illness has some influence on the extent of the involvement of the motor and premotor convolutions and the corresponding lesions in the pyramidal tracts of the internal capsule and cerebral peduncles. The duration and progress of the amyotrophic lateral sclerosis in the 5 cases of severe involvement ranged from five months to four years: in 1 case, five months; in 1 case, one and a half years; in 2 cases, two years, and in 1 case, four years. The duration of the disease in the cases of less severe disease was between two and eight years: in 1 case, one year; in 2 cases, two years; in 2 cases, three years; in 1 case, six years, and in 1 case, eight years. From this it may safely be stated that the length of the illness does not have any influence on the severity and extent of the pathologic process. Analysis of the ages in this group, the detailed figures for which are not included in this presentation, shows that age has no effect on the extent of the lesions. Some clinicians might disagree with the diagnosis of amyotrophic lateral sclerosis in cases in which the illness lasted longer than three or four years. The experience of a number of investigators and the observations in the present and in other cases prove conclusively that patients suffering from amyotrophic lateral sclerosis may survive for a period longer than three to four years.

Cases of Amyotrophic Lateral Sclerosis in Which the Pathologic Process Extended from the Cerebral Peduncles (2 cases).—It should be

emphasized that no instances were found in which the pathologic process originated in the pyramidal parts of the internal capsule. In the 2 cases in which the process began in the peduncles the demyelination was slight.

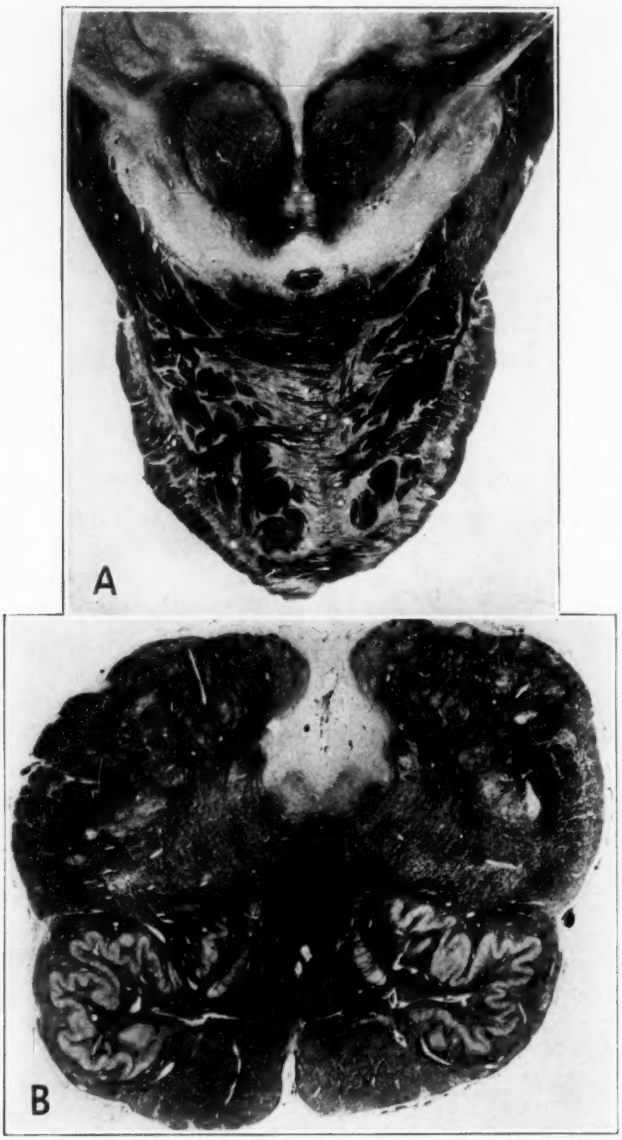

Fig. 4.—Case without cortical involvement. Notice the demyelination in the right peduncle (*A*). In the left peduncle destruction of myelin could easily be detected with higher magnifications. Below the peduncles there was demyelination of both pyramids as seen in the medulla oblongata (*B*). Myelin sheath stain.

In 1 of these cases both peduncles were involved, and in the other only the right peduncle was implicated. This could be demonstrated by the myelin sheath, Spielmeyer (fig. 4 *A*), Marchi and sudan III methods

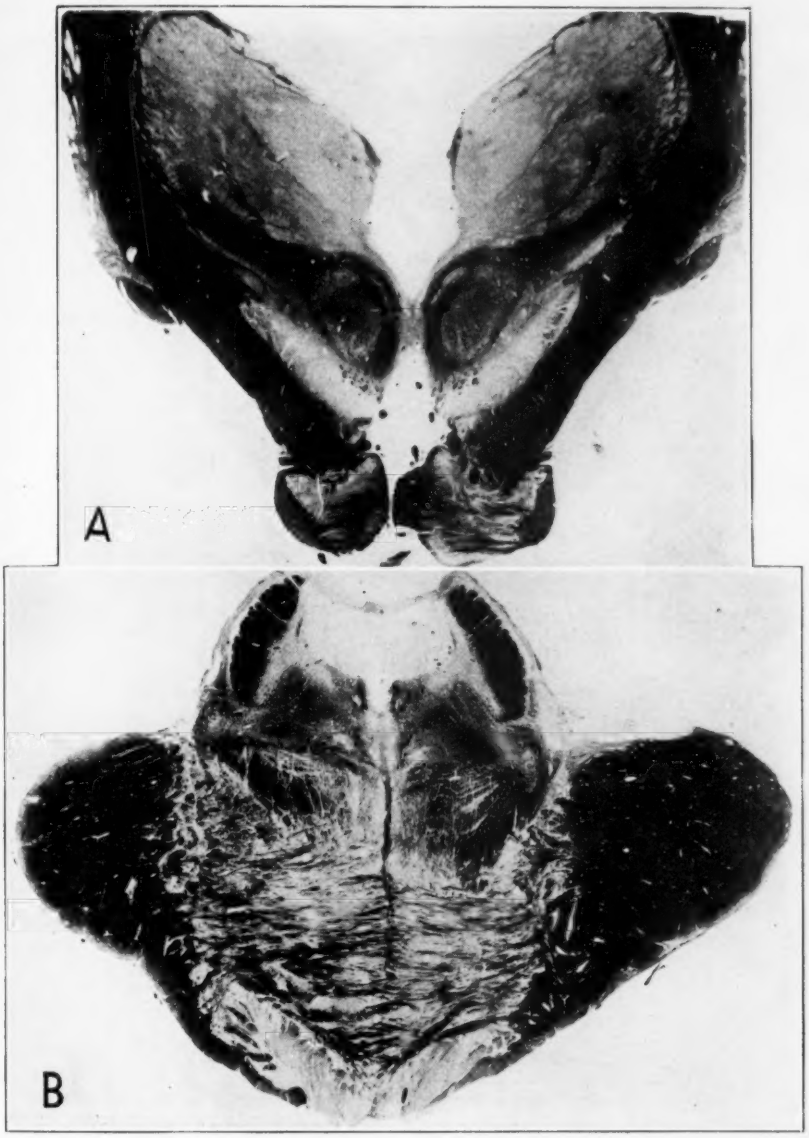

Fig. 5.—Case without cortical involvement. (*A*) Absence of demyelination in the cerebral peduncles. (*B*) Beginning of demyelination in the pons. From this point distally the pyramidal tracts were demyelinated. Myelin sheath stain.

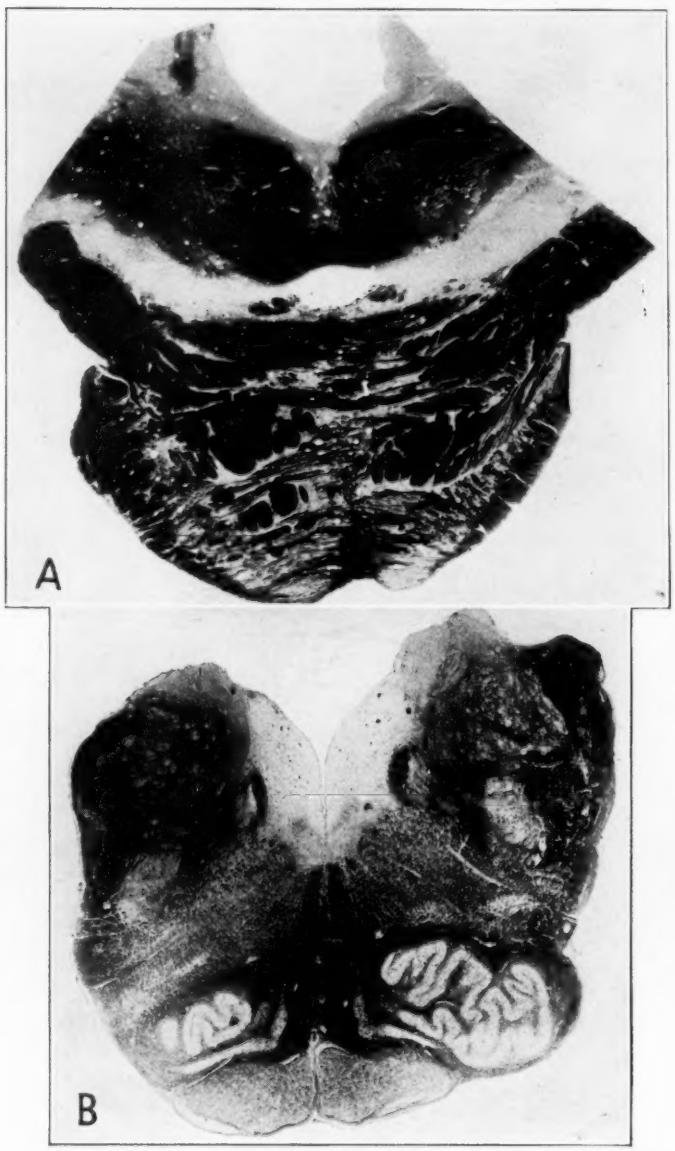

Fig. 6.—Case without cortical involvement, with the process beginning in the medulla oblongata. (*A*) Note the absence of demyelination of the peduncles and pyramids. Spielmeyer method.

(*B*) The demyelination of the pyramids began at this level. Myelin sheath stain.

but was seen best with the last two stains. The demyelination became more marked in the pons and attained its maximum intensity in the medulla oblongata (fig. 4 *B*) and the spinal cord. The ventrolateral tracts (cerebellar and spinothalamic) were involved in both instances. The motor and premotor convolutions were spared. The duration of the illness was two and nine years, respectively.

Cases of Amyotrophic Lateral Sclerosis in Which the Pathologic Process Was Traced from the Pons (7 cases).—Seven cases comprised

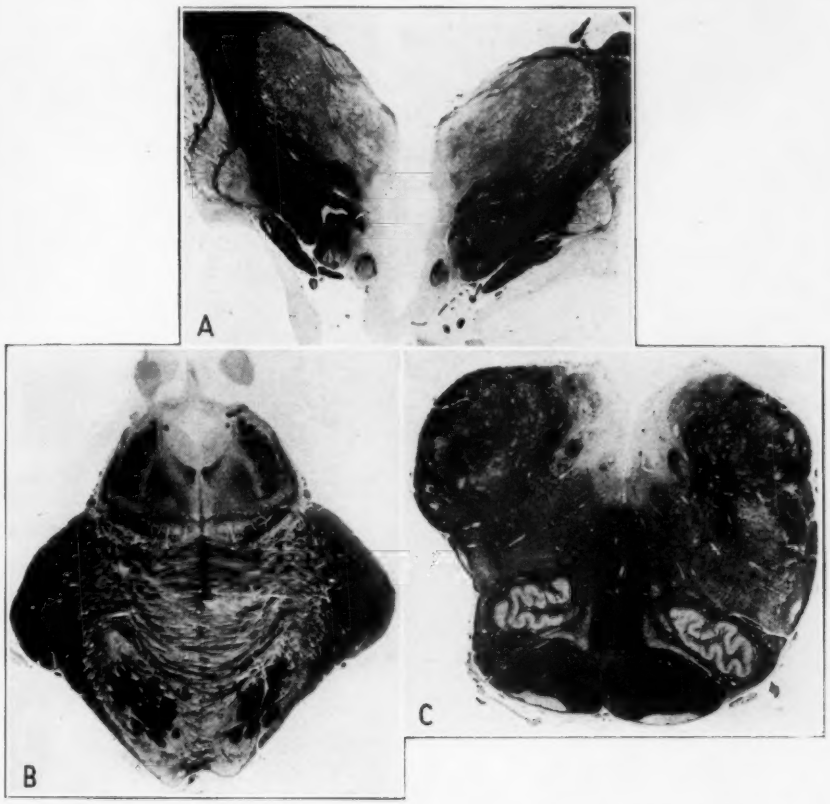

Fig. 7.—Case without cortical involvement. Note the absence of demyelination in the internal capsule (*A*), in the pyramids of the pons (*B*) and in the medulla oblongata (*C*). Myelin sheath stain.

this group. In 2 there was occasional dropping out or chromatolysis of a giant pyramidal cell of Betz in the motor cortex. In no instance was demyelination or disintegration of single myelinated fibers detected with the myelin sheath, the Spielmeyer, the Marchi or the sudan III method in the internal capsule or in the peduncles (fig. 5 *A*). The degeneration began in the pons (fig. 5 *B*) and was most extensive in the medulla oblongata and the spinal cord.

The ventrolateral tracts of the spinal cord (spinocerebellar and spinothalamic, etc.) were found involved in the myelin sheath, Spielmeyer, sudan III and Marchi preparations in 3 cases. The direct pyramidal

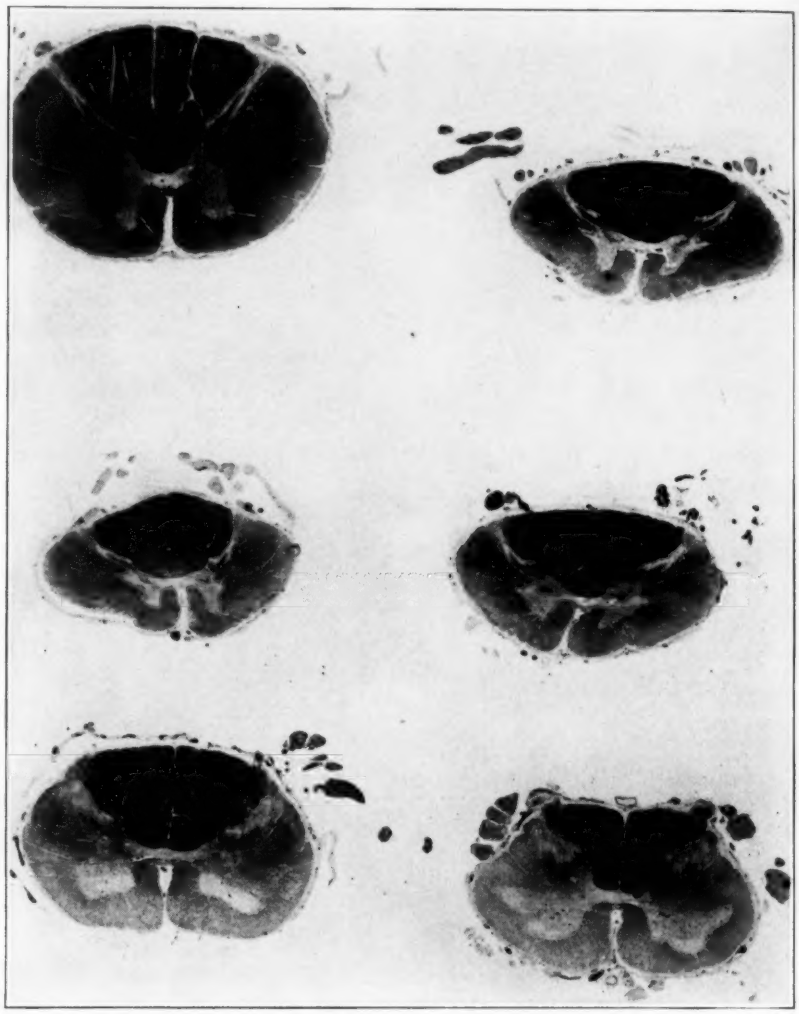

Fig. 8.—Case without cortical involvement. Sections through various regions of the spinal cord, showing demyelination of the ventrolateral tracts. The most extensive demyelination is present in the lower dorsal and the lumbosacral regions. Notice that in the high cervical region the demyelination is not extensive. Myelin sheath stain.

tracts were not affected in 2 cases. The illness lasted six months in 1 case, one year in 2 cases, one and a half years in 1 case, two years in 2 cases and three years in 1 case.

Cases of Amyotrophic Lateral Sclerosis in Which the Pathologic Process Extended from the Medulla Oblongata (12 cases).—Twelve cases belonged to this group. Occasional chromatolysis and dropping out of the giant pyramidal cells of Betz were found in 2 instances. The fibers of the pyramidal tracts in the internal capsule, peduncles and pons were completely intact in all cases (fig. 6 *A*). The demyelination of the pyramids began in the medulla oblongata (fig. 6 *B*), above the decussation in 4 instances (fig. 6 *B*) and below the decussation in 8 instances. The degeneration was most pronounced in the spinal cord. The ventrolateral tracts (spinocerebellar, spinothalamic and others) were involved in 6 instances, while the direct pyramidal tracts were spared in 2 instances. The posterior columns were affected in 4 cases, 2 of which had been previously reported by Davison and Wechsler.[16] The duration of the illness was one and a half years in 2 cases, two years in 4 cases, three years in 2 cases, four years in 1 case, five and a half years in 1 case, seven years in 1 case and eight years in 1 case.

Cases of Amyotrophic Lateral Sclerosis in Which the Pathologic Process Had Its Origin in the Spinal Cord (4 cases).—In the 4 cases of this group involvement of the motor cortex and the pyramidal pathways before they reached the spinal cord could not be demonstrated by any of the staining methods which show early degeneration (fig. 7 *A*, *B* and *C*). The demyelination of the indirect and direct pyramidal tracts in the spinal cord was noted in all instances below the cervical region (fig. 8). Some of the other ventrolateral tracts, such as the spinocerebellar and the spinothalamic, were partially involved in only 1 case. The illness lasted one year in 1 case and two years in 3 cases.

Cases in Which Only the Spinal Cord Was Obtained (5 cases).—These 5 cases are not of any aid in determining the point of origin of the lesion of the pyramidal tract. In 3 instances the other ventrolateral tracts were also partially involved. The duration of the illness was six months in 1 case (that of a patient who had marked bulbar symptoms with mental confusion), one and a half years in 3 cases and two years in 1 case.

COMMENT

A number of facts which stand out clearly in this study justify certain general conclusions. These may have some bearing on the understanding of amyotrophic lateral sclerosis from the etiologic and the pathogenetic point of view.

The present investigation shows conclusively that disease of the upper motor neuron originates in the giant pyramidal cells of Betz in

16. Davison, C., and Wechsler, I. S.: Amyotrophic Lateral Sclerosis with Involvement of the Posterior Column and Sensory Disturbances, Arch. Neurol. & Psychiat. **35**:229 (Feb.) 1936.

only about one third of the cases. The extensive degeneration of the pyramidal pathway, even in these instances, did not become visible until it reached the pons or the medulla oblongata. The lack of extensive demyelination observed in the internal capsule and cerebral peduncles can be accounted for by the incomplete destruction of the giant pyramidal cells of Betz. The complete absence of demyelination in these regions and in the pons cannot be explained on the same basis. It is therefore permitted to conclude that the causative agent of amyotrophic lateral sclerosis, whatever its nature—endogenous or exogenous (chemical, metabolic, virus, vitamin deficiency, vascular disease or abiotrophy[?])—has a predilection for attacking the upper motor neuron, either at its point of origin (motor cortex) or anywhere along its course in the pyramidal pathway, especially in the pons, the medulla oblongata or the spinal cord. The involvement of this efferent tract in the brain stem and spinal cord is not altogether a descending degeneration, as is believed by some observers, but is to a great extent a primary disturbance of the pyramidal pathway. The glia stains (Holzer method) especially help in the clarification of this fact. In amyotrophic lateral sclerosis the involved pathways in the brain stem, especially in the spinal cord, show more diffuse and less intense gliosis than is seen in descending degeneration following an extensive cortical or capsular lesion (fig. 9 *A* and *B*). In descending degeneration following a cerebrovascular insult the gliosis is limited to the pyramidal tract (fig. 9 *B*) and is usually intense (fig. 10 *B*). In amyotrophic lateral sclerosis the gliosis is less intense (figs. 9 *A* and 10 *A*) and is usually present also in other ventrolateral tracts (fig. 11). The instances of amyotrophic lateral sclerosis without cortical, capsular or peduncular involvement are further evidence that the causative agent affects primarily the pyramidal pathway anywhere along its course, especially in the brain stem. Even in the cases in which the process started in the pons, the most extensive demyelination was seen in the medulla oblongata and the spinal cord. The involvement of the motor nuclei of the cranial nerves in the brain stem is not sufficient to account for the massive demyelination of the pyramidal tracts in the medulla oblongata and spinal cord. As further proof that the causative agent may affect the pyramidal pathway anywhere along its course is the concomitant involvement in 21 cases of other ventrolateral pathways (spinocerebellar, spinothalamic, etc.) in the spinal cord. This seems to indicate that the agent in amyotrophic lateral sclerosis also attacks other pathways, although its predilection is preponderantly for the upper and lower motor neurons, as attested by the more frequent and more extensive involvement of these two components.

Amyotrophic lateral sclerosis may, therefore, be divided anatomically into forms in which the upper motor neuron lesion may originate in the

motor cortex, the peduncles, the pons, the medulla oblongata or the spinal cord. As already stated, the largest number of cases belongs to the group in which the lesion was traced from the pons and the medulla oblongata.

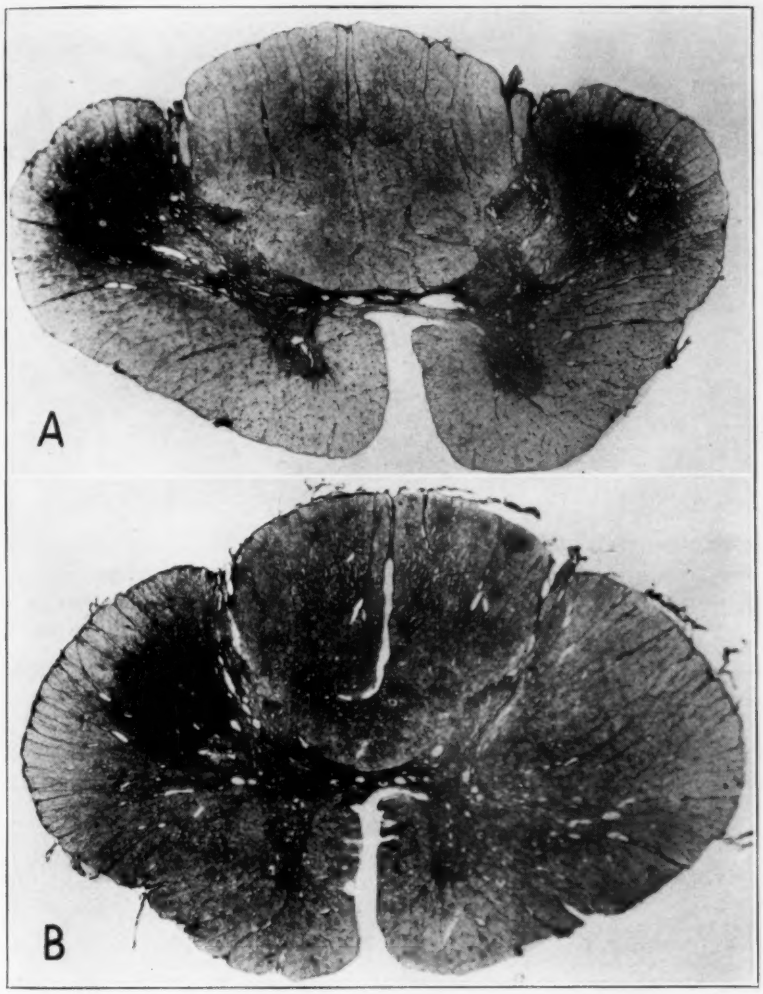

Fig. 9.—(*A*) Gliosis in both crossed pyramidal tracts in a case of amyotrophic lateral sclerosis. Note absence of gliosis within the direct pyramidal tract. Compare with *B*. (*B*) Dense gliosis of the left crossed pyramidal tract following descending degeneration. Holzer stain.

Further observation of the material presented disclosed in 6 cases an inflammatory reaction in the affected regions, instead of the typical pathologic process of amyotrophic lateral sclerosis, which is analogous

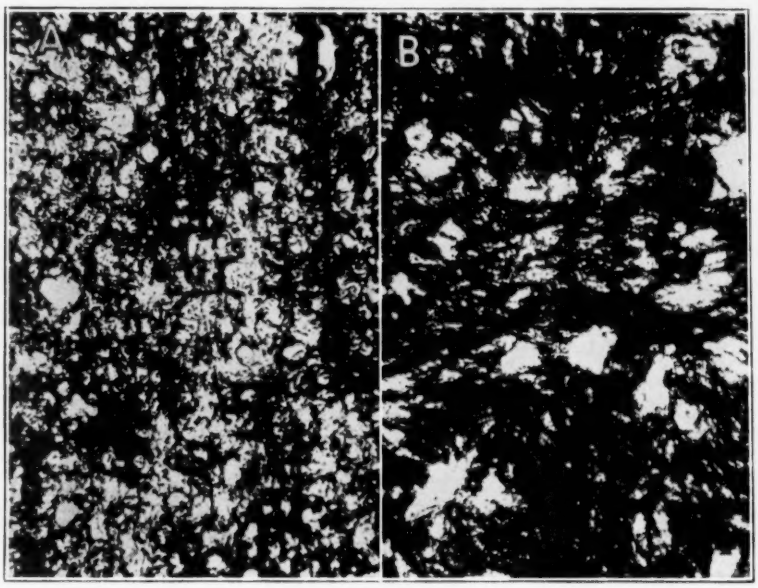

Fig. 10.—(*A*) Gliosis in the crossed pyramidal tract in a case of amyotrophic lateral sclerosis. Compare with *B*. (*B*) Gliosis of the crossed pyramidal tract in a case of descending degeneration. Holzer stain; × 266.

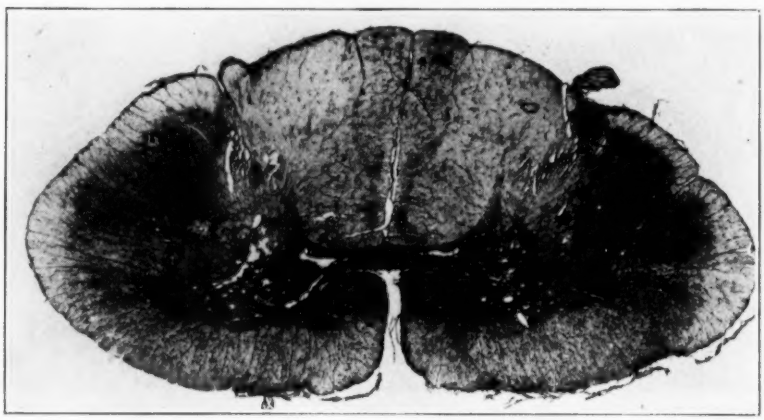

Fig. 11.—Gliosis of the crossed and part of the direct pyramidal tract in a case of amyotrophic lateral sclerosis. Note slight gliosis of other ventrolateral tracts. Holzer stain.

to the so-called degenerative changes seen in intoxication. As is well known, Wimmer [17] and others have described cases of amyotrophic lateral sclerosis as sequelae of encephalitis lethargica. The previous existence of syphilis or encephalitis lethargica in the aforementioned 6 cases was definitely excluded. From a pathologic point of view, amyotrophic lateral sclerosis can, therefore, be classified as a degenerative and an inflammatory process, the so-called degenerative process being the more prevalent.

Wechsler,[18] on the basis of studies on the effect of vitamin E in amyotrophic lateral sclerosis, expressed the belief that there are at least three or four varieties of the amyotrophic lateral sclerosis syndrome. These include the inflammatory type as described by Wimmer,[17] a type, represented by a small group of cases, which results from vascular disease, possibly syphilitic, and a third, or degenerative, type, the only one apparently which responds to vitamin E therapy. In our groups there were no cases of amyotrophic lateral sclerosis resulting from atherosclerosis or syphilis. Undoubtedly a few such instances do exist, and I have encountered them clinically. It is doubtful whether in all cases of so-called degenerative amyotrophic lateral sclerosis there is a response to vitamin E therapy. In 3 of the cases in which necropsy was performed there was no clinical response to such therapy. However, it is possible that the patients were not treated adequately. Further and later observations will clarify the issue. The recovery from the bulbar signs and the lack of improvement in the pseudobulbar signs, as reported by Wechsler in studies on vitamin E therapy, shed further light on the variability of types of amyotrophic lateral sclerosis. Apparently, vitamin E therapy has clinically an effect on the motor nuclei, but not on the pyramidal pathways. Wechsler [18] is possibly correct, and neuropathologists have for a long time been dissatisfied with the term degenerative disease of the central nervous system. The term is, and was, used only because of lack of adequate knowledge concerning the etiologic agent. Vitamin E deficiency, such as that observed in some cases of amyotrophic lateral sclerosis, may account for some, but certainly not all, the so-called degenerative diseases of the central nervous system.

Some observers have expressed the belief that the extension of the pathologic process to the motor cortex, internal capsule and peduncles depends on the duration of the illness. With the exception of the 3 instances in the group with involvement of the motor cortex in which

17. Wimmer, A.: Chronic Epidemic Encephalitis, London, William Heinemann, 1924.

18. Wechsler, I. S.: The Treatment of Amyotrophic Lateral Sclerosis with Vitamin E, Am. J. M. Sc. **200**:765, 1940.

the illness lasted four, six and eight years respectively, the duration of the illness did not vary much from that in the groups in which the process started in the brain stem or the spinal cord.

CONCLUSIONS

Forty-two cases of amyotrophic lateral sclerosis were studied histopathologically with reference to the origin and extent of the lesion of the upper motor neuron. Disease of the upper motor neuron originated in the giant pyramidal cells of Betz in only about one third of the cases, while in the remaining two thirds the pyramidal tracts became involved in the pons, the medulla oblongata or the spinal cord. The duration of the illness had no influence on the extent of involvement of the giant pyramidal cells of Betz.

The causative agent of amyotrophic lateral sclerosis has a predilection for attacking the upper motor neuron either at its point of origin (the motor cortex) or anywhere along its course, but chiefly in the brain stem and the spinal cord. As further proof that the pyramidal pathways become involved anywhere along their course is the concomitant implication of other ventrolateral tracts of the spinal cord, for example, the spinothalamic and the spinocerebellar, in 21, or one half, of the cases.

From the point of view of the lesion of the upper motor neuron, amyotrophic lateral sclerosis can be classified anatomically into forms originating in the cortex, the peduncle, the brain stem and the spinal cord. Pathologically, 36 cases belong to the degenerative and 6 to the inflammatory type.

RUPTURED ANEURYSM OF THE LEFT ANTERIOR CEREBRAL ARTERY WITH PRODUCTION OF IPSILATERAL CEREBRAL SIGNS

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AND
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The subjects of intracranial aneurysm with rupture producing subarachnoid hemorrhage and of ipsilateral cerebral signs produced by an intracranial mass lesion have separately been well represented in the literature. The occurrence of ipsilateral cerebral signs resulting from a ruptured aneurysm of the left anterior cerebral artery, with additional pathologic data, is sufficiently unique, we feel, to justify recording of the case.

REPORT OF A CASE

History.—J. D., a man aged 54, was admitted to the Doctors Hospital on Dec. 23, 1940, to the service of one of us (A. A. B.).

For five months prior to admission he had been suffering from severe periodic frontal headaches. There had been a personality change characterized by periods of depression, indifference and emotional instability. For several weeks his wife noted that he walked with a dragging, shifting gait, so that she asked him to "lift his feet." During the two weeks prior to admission he had occasionally experienced sharp, shooting pain in the left frontotemporal region. On December 19 he complained of an unusually severe headache. He lay down and started to vomit, the vomiting being projectile in character, and broke out into profuse perspiration. The following day the vomiting recurred and the headache persisted. He became increasingly apathetic, forgetful and listless.

There had been no history of recent illness. He had, however, had financial reverses during the past few years. He had been married for ten years to his brother's widow. There had been no children of this marriage, and the marital relations had been very unsatisfactory.

Examination.—The patient was apathetic and unconcerned about his condition. He answered questions sparingly and occasionally became drowsy and apparently fell asleep. Memory for recent and remote events was markedly impaired. There was no speech defect, but he seemed to have difficulty in comprehending the import of questions put to him, and the examination was difficult because of his failure to respond promptly and intelligently to questions regarding sensation, coordination and the like. There was inequality of the palpebral fissures, the right being smaller than the left. The pupils were unequal in size, the right being smaller

From the Doctors Hospital.

* From the John Leonard Eckel Laboratory of Neuropathology, the University of Pennsylvania Graduate School of Medicine.

than the left. They responded sluggishly to light but promptly in accommodation. Examination of the fundi showed slight haziness of both disks but no choking. There was no disturbance of sensation over the face. Mild facial weakness of central type was present on the left side. The remaining cranial nerves were normal. There was some motor weakness in the left arm and left leg. The biceps and triceps reflexes in the left arm were definitely stronger than those in the right. The Hoffmann sign was not present. The abdominal reflexes were normal on the right side but were diminished and readily exhaustible on the left. There was eversion of the left leg, and a mild static Babinski sign was present on the left. The knee jerks could be obtained only by means of Jendrassik's reenforcement. Both ankle jerks were greatly diminished. The Babinski phenomenon could not be elicited. There was no disturbance of coordination in the upper limbs as manifested by the various tests. The heel to knee test, however, was poorly performed with the left leg. In addition, there was some flabbiness of the calf muscles of the left leg as compared with those of the right. Although sensation was difficult to evaluate because of the patient's mental state, there was evidence after frequent testing that diminution of sensation to pinprick was present over the entire left half of the body except the face. Stereognostic sense was not disturbed on either side. Apraxia could not be brought out. There was slight nuchal resistance, and positive Kernig and Brudzinski signs could be obtained bilaterally.

The temperature on admission was 102 F. Examination of the ears, nose and throat revealed chronic pansinusitis with a superimposed acute infection.

On the day following admission, December 24, lumbar puncture revealed an initial pressure of 350 mm. of cerebrospinal fluid. The fluid was uniformly blood tinged. A total of 5 cc. was removed for study, with a final pressure of 210 mm. of fluid. A tentative diagnosis of cerebral tumor with hemorrhage or ruptured cerebral aneurysm was made.

Laboratory Data.—A blood count, made on December 23, revealed 74.5 Gm. of hemoglobin per hundred cubic centimeters, or 94 per cent, 4,870,000 red cells and 8,600 white cells, with 81 mature neutrophils, 15 per cent lymphocytes and 4 per cent monocytes.

Chemical analysis of the blood on December 24, revealed 11 mg. of urea nitrogen, and 71 mg. of sugar per hundred cubic centimeters.

Examination of the urine, on December 24, revealed that it was amber and slightly cloudy, with an alkaline reaction and a specific gravity of 1.015, a negative reaction for albumin and sugar and the presence of a few epithelial cells, 1 to 2 white blood cells and amorphous crystals.

Suitable roentgenograms of the skull could not be obtained during the patient's stay in the hospital. A single lateral view of the skull which had been taken with roentgenograms of the sinuses previous to admission to the hospital revealed calcification of the pineal gland, fluffy calcification in the parieto-occipital region and some calcification lying, as it appeared, within and slightly above the sella turcica (fig. 1).

Course of Illness.—At about 10:30 p. m. on December 24 a generalized convulsive seizure developed. The patient was comatose, and respirations were of the Cheyne-Stokes variety. Marked pulmonary edema was present. The temperature increased to 104.6 F. and rose steadily until his death, when it was 106.4 F. There were marked opisthotonos and occasional clonic twitchings of the extremities, and the left arm and hand were maintained in the position of flexion. The eyeballs deviated up and to the left. A ventricular puncture was performed

by Dr. Robert Groff, and the cerebrospinal fluid escaped under moderate pressure and was uniformly blood tinged. The patient failed to respond and remained unconscious until he died, on December 25. The clinical diagnosis at that time was ruptured basal aneurysm with subarachnoid hemorrhage.

Autopsy.—During the removal of the brain from the skull a tumor was disclosed lying over the mesial portion of the left sphenoid ridge and impinging on the optic chiasm and the left optic nerve. This mass measured 2.7 cm. in diameter and had a thick, glistening capsule, which had been ruptured at one point communicating with the subarachnoid space and the posterior portion of the orbital gyrus. Grossly it appeared much like a meningioma but on sectioning proved to be a ruptured aneurysm.

Gross Examination: The mass which was removed from the mesial aspect of the left sphenoid ridge was attached by a dural pedicle. This mass was very firm, and its surface had several smooth nodules. Attached to the inferior portion of the capsule by loose strands, but not an integral part of it, was the left olfactory

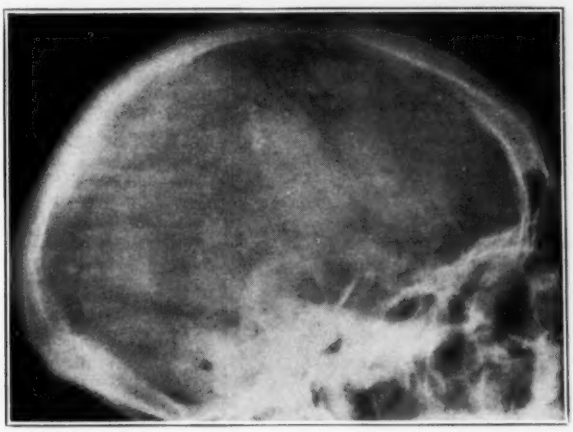

Fig. 1.—Lateral view of the skull, showing calcified pineal body, fluffy calcification in the parieto-occipital area and crescentic calcification lying immediately above the sella turcica.

bulb. On the superior aspect of the lesion was a small cystic portion, measuring 0.7 cm., which communicated with an opening in the capsule. Section through the mass showed that the capsule consisted mainly of dura and contained a solid portion, which cut with considerable resistance, and a cystic portion, which contained fluid blood. There was calcium in the solid portion of the lesion (fig. 2).

The brain was edematous and the gyri somewhat flattened. There was generalized subarachnoid hemorrhage, most marked over the frontal lobes, in the sylvian fissures and in the basal cisterns. The hippocampal gyrus and the posterior portion of the orbital gyrus of the left cerebral hemisphere showed an indentation and hemorrhagic necrosis, which represented the area compressed by the mass over the sphenoid ridge. Sections of the pons, medulla and cerebrum revealed congestion. Coronal section through the frontal lobes showed that the left hemisphere was larger than the right and the centrum ovale of the left hemisphere edematous. The lateral ventricles were normal in size, and the left contained blood.

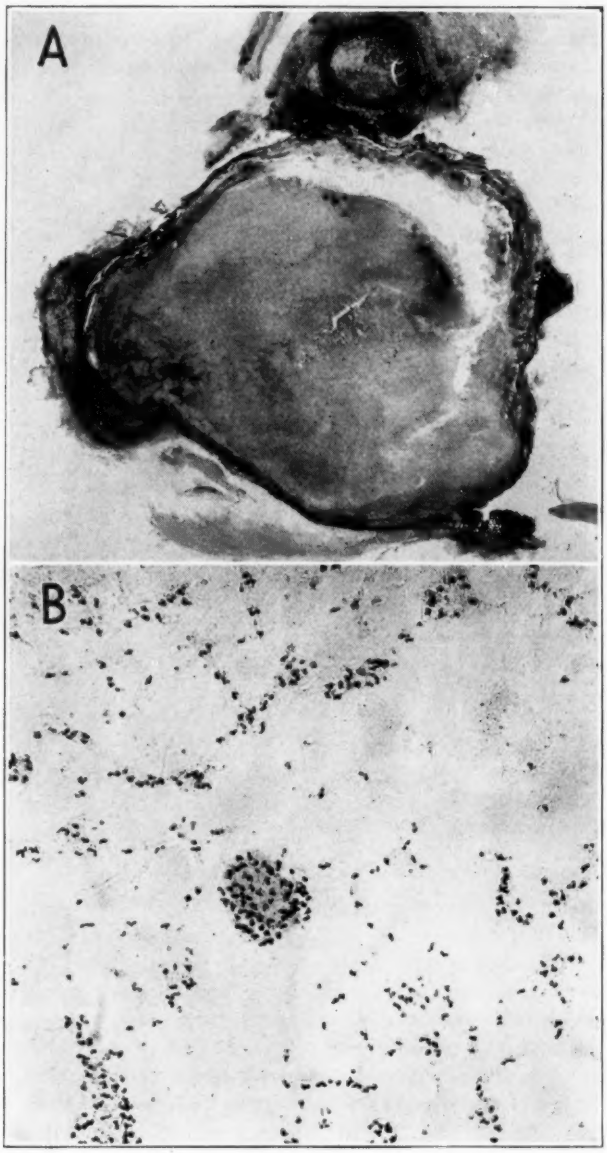

Fig. 2.—(*A*) Section through the aneurysmal sac, showing the thick dural capsule, with point of rupture and the solid hyalinized portion, and the upper aspect of the sac, containing free, unorganized blood. There is considerable calcium, as shown by the dark-stained granules to the left and near the center of the solid contents of the sac. Toluidine blue stain; × 3.6.

(*B*) Section showing hyalinized material which has been canalized, the canaliculi containing free blood. Toluidine blue stain; × 160.

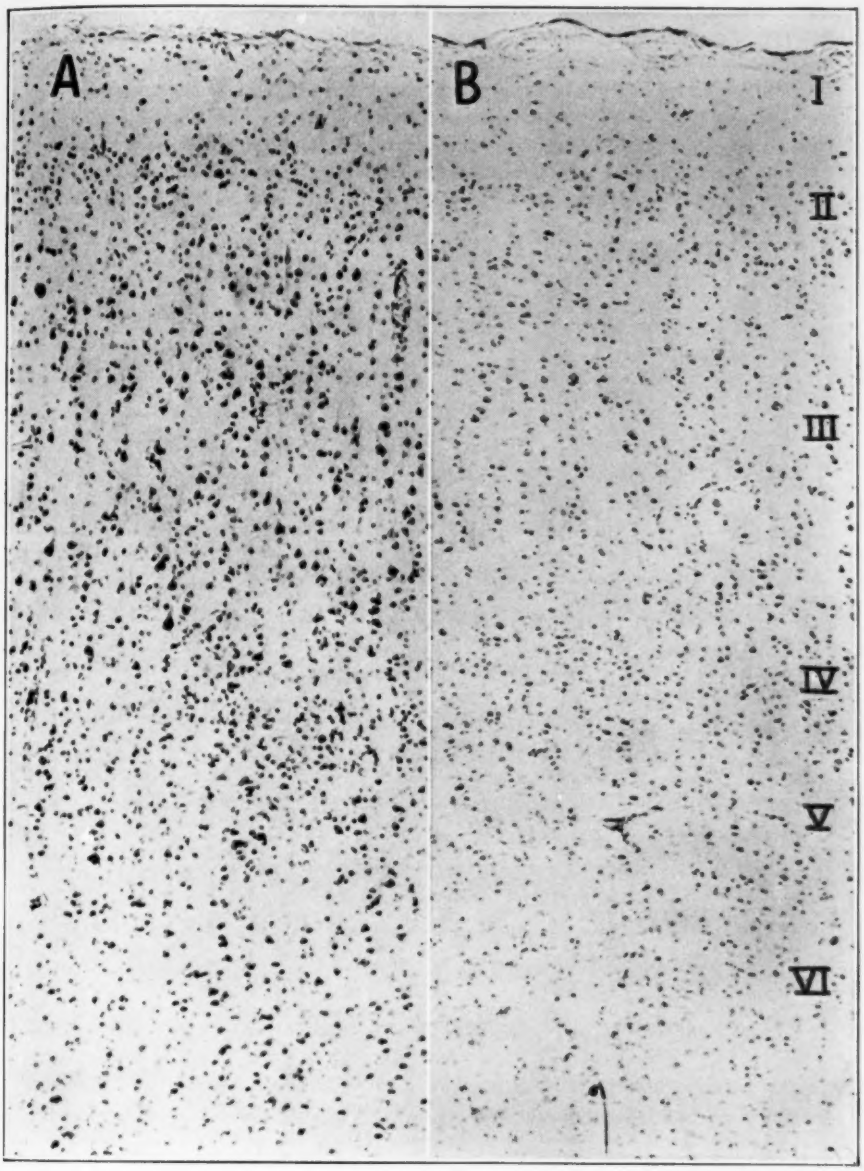

Fig. 3.—(*A*) Section through the granular cortex of the right frontal lobe, showing normal cellular architecture.

(*B*) Section through the corresponding cortex of the left frontal lobe, indicating the marked loss of ganglion cells, the chronic and severe ganglion cell disease and the "washing out" of the ground substance.

Toluidine blue stain; × 70.

Microscopic Examination: Microscopic examination of the mass described grossly as an aneurysm revealed a thick capsule composed of dura and fibrous connective tissue. The elements of the original vessel walls could not be distinguished. The greater part of the contents of the sac consisted of hyalinized material which had been canalized. The canaliculi varied in size from the diameter of a capillary to that of a good-sized venous channel. They were filled with blood. At the inferior aspect of the lesion, and comprising about one fourth of the contents of the sac, was free, unhemolyzed blood, which communicated with the exterior of the sac through a defect in the dural envelop. At the periphery

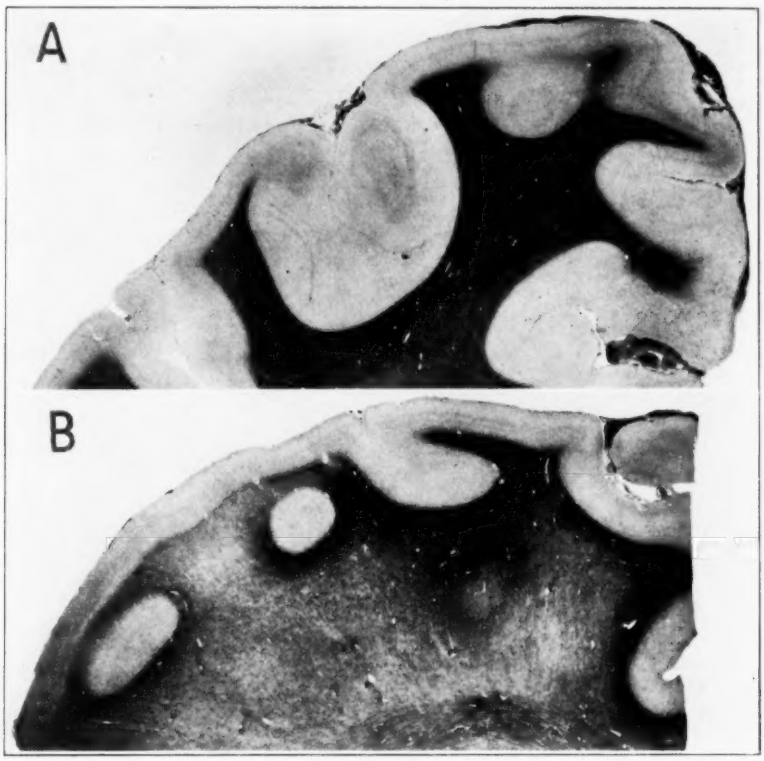

Fig. 4.—(*A*) Section of the right frontal lobe, showing normal subcortex and cortex.

(*B*) Section through a corresponding area of the left frontal lobe, showing diffuse partial demyelination and swelling of the subcortex.

Weil stain for myelin sheaths; × 2.

of this lake of blood, and constituting the inner wall of the sac, were numerous young fibroblasts extending into the blood mass. At several places along the inner aspect of the fibrous sac there was considerable deposition of calcium. Adherent to the outer aspect of the sac, at the point of rupture, was a mass of cells composed of polymorphonuclear leukocytes, pigment-laden histiocytes and fibrous connective tissue cells. Many small vessels studded the external aspect of the sac.

Examination of the left frontal lobe revealed free blood and pigment-laden histiocytes in the dilated subarachnoid space. The ganglion cells of the cortex were widely separated, giving the appearance of a diminution in number. The ground substance seemed washed out. In many areas the ganglion cells were puffed out and showed marked cloudy swelling, as well as severe cell disease (fig. 3). Many shadow cells were encountered, and acellular foci were frequent in the cortex. The small vessels were prominent and contained many polymorphonuclear cells, and the perivascular spaces about the small and medium-sized vessels were dilated.

Fig. 5.—Myelin sheath stain (Weil) showing the marked notching of the right peduncle. × 2.5.

The posterior portion of the left orbital gyrus showed several ischemic infarcts, in which vascularization had taken place. In addition, several areas showed softening and hemorrhagic necrosis of tissue.

The subcortex of the left frontal lobe and of the remaining portions of the left cerebral hemisphere was greatly swollen. The ground substance was spongy, and there was considerable increase of glia, particularly astrocytes. The latter were swollen, and even with toluidine blue the cytoplasm and processes could be easily distinguished.

The right frontal lobe revealed small infarctions and hemorrhages in the posterior limb of the orbital gyrus similar to those seen on the opposite side,

but not as extensive. There was considerable marginal gliosis. The remainder of the right cerebral cortex failed to show the profound changes seen in the left cerebral cortex. The subcortex was not swollen, and a counterpart of the astrocytic proliferation seen in the opposite cerebral hemisphere was not to be found. The vessels, although prominent, failed to show the amount of dilatation of the perivascular spaces seen in the left cerebral hemisphere. There was free blood in the subarachnoid space over the right frontal lobe.

Some of the cerebellar folia showed dropping out of cells in the Purkinje cell layer. Occasional Purkinje cells were pyknotic, and in several areas their dendritic processes were stained well into the molecular layer. There was considerable free blood in the basal subarachnoid space.

The inferior olive on both sides showed diminution in the number of cells, and many of those remaining had undergone advanced fatty degeneration.

In the pons the vessels were congested, particularly the venules and veins, which were tremendously enlarged, as though the venous return was prevented by external pressure.

Sections of the left frontal lobe stained for myelin sheaths showed swelling of the subcortex and thinning of the cortex, with moderate diffuse demyelination of the white matter. This obtained to a lesser degree in the remainder of the left hemisphere. The right side showed normal staining of myelin sheaths (fig. 4).

The pes pedunculi on the right side had a deep indentation corresponding to the position of the free edge of the tentorium (fig. 5).

The optic chiasm and optic nerves showed no demyelination.

The large vessels at the base of the brain displayed moderate intimal thickening. Early hyaline change of the medium-sized vessels could be seen in the cortex and in the subcortical ganglia.

Microscopic Diagnosis.—The diagnosis was (1) "Berry" aneurysm of left anterior cerebral artery and rupture with subarachnoid hemorrhage, (2) swelling of the left cerebral hemisphere, (3) severe disease of the ganglion cells in left frontal lobe, (4) tentorial notching of the right crus and (5) early cerebral arteriosclerosis.

COMMENT

There are several points of interest in this case, both clinically and pathologically. For several months prior to the acute phase of the patient's illness there had been mental and emotional manifestations, which had been attributed to his financial and marital difficulties. There were no specific data having localizing significance other than perhaps the fact that during the last few weeks of his illness there was persistent shooting pain confined to the left side of the head over the frontoparietal region. In the light of the swelling of the left cerebral hemisphere, particularly in the frontal lobe, and the marked cellular disturbance in this region, in all probability due to a deficient circulation in the distribution of the involved left anterior cerebral artery, the mental phenomena can be explained on the basis of these factors.

The acute episode was characterized by symptoms indicating an abrupt onset of increased intracranial pressure. The objective neurologic signs, although poorly defined, pointed to a lesion involving the

right parietomotor area. Even with the obtunding of the sensorium, it was possible to note a sensory disturbance on the left side consisting of diminution of pain sensation, increased reflexes in the left arm as compared with those in the right, diminished abdominal reflexes on the left, eversion of the left leg with a mild static Babinski sign, disturbance of coordination and motor power in the left leg and a central type of facial weakness on the left. These findings indicated a lesion of the right hemisphere, and the only plausible explanation for their existence was the notching of the right crus resulting from pressure produced by jamming of the right peduncle against the free edge of the tentorium by the edematous left cerebral hemisphere, as illustrated in figure 5. Numerous observers [1] have noted ipsilateral hemiplegia resulting from an intracranial lesion which has caused compression of the contralateral crus. Rand [2] reported ipsilateral hemiplegia in cases of intracranial hemorrhage in which a similar mechanism was involved. Moore and Stern [3] called attention to marked notching of the contralateral crus in cases of supratentorial tumor associated with swelling of the brain. In these reports there were marked evidences of hemiplegia. In the case presented here only mild sensory and motor changes involving the left side of the body were present.

The cases described by Hoen [4] more closely paralleled our case in that ipsilateral weakness was present, as well as paralysis. He offered the same explanation of the mechanism as that given by the other observers. Reid,[5] in an excellent article, discussed the clinical, pathologic and experimental aspects of cerebral herniation through the incisura tentorii and explained the occurrence of ipsilateral dilated pupil and palsy of the third nerve and hemiplegia by herniation of the hippocampal gyrus through the incisura, causing pressure on the structures of the

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2. Rand, C. W.: Significance of Dilated Pupil on Homolateral Hemiplegic Side in Cases of Intracranial Hemorrhage Following Head Injuries: Report of Seven Cases, Arch. Surg. **18**:1176 (April) 1929.

3. Moore, M. T., and Stern, K.: Vascular Lesions in the Brain Stem and Occipital Lobe Occurring in Association with Brain Tumors, Brain **61**:70, 1938.

4. Hoen, T. I.: Hémiplégie homolatérale avec lésions intracraniennes, Bull. Assoc. de méd. de langue franç. **1**:353, 1935.

5. Reid, W. L.: Cerebral Herniation Through the Incisure Tentorii, Surgery **8**:756, 1940.

midbrain and notching of the contralateral crus. In the majority of cases reported in which ipsilateral phenomena occurred a supratentorial mass lesion involved the cerebrum itself. In the case reported here, however, the signs were due to a secondary swelling of the cerebral hemisphere consequent to disturbed circulation by an aneurysm of the left anterior cerebral artery.

It has been shown by Dandy [6] that ligation of the left anterior cerebral artery will produce unconsciousness from which the patient does not recover. Poppen [7] further emphasized this and called attention to the fact that if the blood pressure can be maintained this artery can be ligated without disastrous effects. Dandy expressed the belief that the left anterior cerebral artery supplies a center of consciousness located in the left cerebral hemisphere. The mental symptoms shown by our patient may have resulted in part from the disturbed circulation of the left anterior cerebral artery. That a greater degree of disturbed consciousness did not exist can be accounted for by the slow impoverishment of the blood supply, permitting some degree of collateral circulation to take place. The swelling of the left frontal lobe, particularly the mesial aspect, with severe involvement of the ganglion cells undoubtedly was the result of the impaired circulation.

The disturbance in the cerebral architecture consisted of chronic and acute cell changes, indicating two phases, one produced by the slow shutting off of the circulation and the other resulting from rupture of the aneurysmal sac. The swelling of the frontal lobe with diffuse partial demyelination of the subcortex and diffuse gliosis again was indicative of a circulatory deficiency. That other evidences of involvement of the left anterior cerebral artery, such as contralateral motor phenomena and motor aphasia, were not manifest may be attributed to the fact that some circulation still existed and that collateral circulation had been partially established. Apraxia could not be evaluated properly because of the mental hebetude of the patient.

The aneurysm occurred at the bifurcation into the anterior cerebral artery and the anterior communicating artery. According to Richardson and Hyland,[8] "berry" aneurysms of the circle of Willis occur most frequently in the middle cerebral artery at or about its first bifurcation and in the anterior cerebral artery. They take up in excellent and elaborate detail the many aspects of intracranial aneurysm and sub-

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6. Dandy, W. E.: The Brain, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, chap. 1, p. 51.

7. Poppen, J. L.: Ligation of the Left Anterior Cerebral Artery: Its Hazards and Means of Avoidance of Its Complications, Arch. Neurol. & Psychiat. **41**:495 (March) 1939.

8. Richardson, J. C., and Hyland, H. H.: Intracranial Aneurysms, Medicine **20**:1, 1941.

arachnoid hemorrhage and discuss the clinical, pathologic and etiologic factors involved. It would, therefore, be redundant to dilate here on these questions pertaining to aneurysm. The aneurysm occurring in our case was undoubtedly of developmental origin.

SUMMARY

A case of a moderately large ruptured saccular "berry" aneurysm of the left anterior cerebral artery occurring in a man of 54 is reported. The disturbed vascular supply resulted in swelling of the left frontal lobe, causing dislocation and herniation of the brain stem through the incisura with resultant notching of the contralateral crus by the free edge of the tentorium, thereby producing ipsilateral cerebral signs. Attention is called to the disturbed state of consciousness and the behavior of the patient both with regard to the problem of differential diagnosis and the explanation to be found in the pathologic state of the cortex and subcortex of the left frontal lobe.

VITAMIN E AND ALPHA TOCOPHEROL THERAPY OF NEUROMUSCULAR AND MUSCULAR DISORDERS

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It has been known for several years that deficiency of vitamin E in the diet is responsible for the production of certain changes in the muscular and neuromuscular systems of experimental animals. Conditions reported to have resulted from such a deficiency are as follows: muscular dystrophy in the rat, guinea pig, rabbit and dog [1]; myopathies, involving especially the nonstriated musculature, in the duck and turkey [2]; encephalomalacia, pareses and cerebellar disorders in the chick [3]; various paralyses in the suckling rat,[4] and pareses in the adult rat, with involvement of the posterior columns, pyramidal tracts and anterior

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1. Goettsch, M., and Pappenheimer, A. M.: Nutritional Muscular Dystrophy in the Guinea Pig and Rabbit, J. Exper. Med. **54**:145 (April) 1931. Morgulis, S., and Spencer, H. C.: A Study of the Dietary Factors Concerned in Nutritional Muscular Dystrophy, J. Nutrition **11**:573 (June) 1936. Pappenheimer, A. M.: The Pathology of Nutritional Muscular Dystrophy in Young Rats, Am. J. Path. **15**:179 (March) 1939. Mackenzie, C. G., and McCollum, E. V.: Vitamin E. and Nutritional Muscular Dystrophy, Science **89**:370 (April 21) 1939. Anderson, H. D.; Elvehjem, C. A., and Gonce, J. E., Jr.: Vitamin E Deficiency in Dogs, Proc. Soc. Exper. Biol. & Med. **42**:750 (Dec.) 1939.

2. Jungherr, E., and Pappenheimer, A. M.: Nutritional Myopathy of the Gizzard in Turkeys, Proc. Soc. Exper. Biol. & Med. **37**:520 (Dec.) 1937.

3. Pappenheimer, A. M., and Goettsch, M.: Cerebellar Disorder in Chicks, Apparently of Nutritional Origin, J. Exper. Med. **53**:11 (Jan.) 1931. Keenan, J. A.; Kline, O. L.; Elvehjem, C. A.; Hart, E. B., and Halpin, J. G.: New Nutritional Factors Required by the Chick, J. Biol. Chem. **103**:671 (Dec.) 1933. Dam, H.; Glavind, J.; Bernth, O., and Hagens, E.: Anti-Encephalomalacia Activity of dl-a-Tocopherol, Nature, London **142**:1157 (Dec. 31) 1938.

4. Evans, H. M., and Burr, G. O.: Development of Paralysis in the Suckling Young of Mothers Deprived of Vitamin E, J. Biol. Chem. **65**:273 (Jan.) 1928. Olcott, H. S.: Paralysis in the Young of Vitamin E Deficient Female Rats, J. Nutrition **15**:221 (March) 1938.

horn cells of the spinal cord.[5] These disturbances can be prevented, and even relieved, by adding to the animal's diet the deficient vitamin or alpha tocopherol, an alcohol having the properties of vitamin E.[6] This substances was first isolated from wheat germ oil, but can now be produced synthetically.[7]

The similarity between the aforementioned conditions and certain diseases of the muscular and neuromuscular systems in man has led to the use of vitamin E and alpha tocopherol in treatment of some of the latter, and a few enthusiastic reports of the efficacy of these preparations have appeared. Vitamin E and alpha tocopherol have been used principally for two conditions which, it happens, are entirely unrelated clinically and pathologically, namely, muscular dystrophy and amyotrophic lateral sclerosis. Reports by Bicknell[8] and Stone[9] were opti-

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7. Evans, H. M.; Emerson, O. H., and Emerson, G. A.: The Isolation from Wheat Germ Oil of an Alcohol, Alpha-Tocopherol, Having the Properties of Vitamin E, J. Biol. Chem. **113**:319 (Feb.) 1936.

8. Bicknell, F.: Vitamin E in the Treatment of Muscular Dystrophies and Nervous Diseases, Lancet **1**:10 (Jan. 6) 1940.

9. Stone, S.: Treatment of Muscular Dystrophies and Allied Conditions: Preliminary Report on the Use of Vitamin E (Wheat Germ Oil), J. A. M. A. **114**:2187 (June 1) 1940.

mistic, as were the original observations of Wechsler,[10] but after a more prolonged period of observation the latter[11] concluded that only a certain proportion of patients, possibly 20 to 30 per cent, show improvement of varying degrees, when synthetic vitamin E is given; many do not improve, and some become worse. He expressed the belief that vitamin E deficiency is but one factor in the causation of amyotrophic lateral sclerosis and vitamin replacement is only one avenue of therapeutic approach. He did, however, stress the fact that administration of vitamin E is the only therapeutic measure which has afforded even the slightest improvement, temporary arrest of progress or remission of amyotrophic lateral sclerosis. More recent observers have failed to reproduce the results noted in the earlier reports.[12]

MATERIAL

Since April 1940 alpha tocopherol[13] and wheat germ oil have been used in the University Hospital in the treatment of muscular and neuromuscular diseases. Nineteen patients with amyotrophic lateral sclerosis, 1 patient with amyotrophic lateral sclerosis associated with syphilis, 5 patients with progressive spinal muscular atrophy, 8 patients with pseudohypertrophic muscular dystrophy and 2 patients with recent extensive poliomyelitis have been treated for a long enough period to warrant reporting their cases.

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10. Wechsler, I. S.: (*a*) Recovery in Amyotrophic Lateral Sclerosis Treated with Tocopherols (Vitamin E): Preliminary Report, J. A. M. A. **114**:948 (March 16) 1940; (*b*) Recovery in Two Cases of Amyotrophic Lateral Sclerosis Treated with Tocopherol (Vitamin E), Arch. Neurol. & Psychiat. **44**:470 (Aug.) 1940; (*c*) The Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Tocopherols), Am. J. M. Sc. **200**:765 (Dec.) 1940.

11. Wechsler, I. S.: Amyotrophic Lateral Sclerosis Treated with Synthetic Vitamin E, J. Nerv. & Ment. Dis. **93**:353 (March) 1941.

12. Alpers, B. J.; Gaskill, H. S., and Cantarow, A.: Effect of Vitamin E on the Muscular Dystrophies, Arch. Neurol. & Psychiat. **45**:364 (Feb.) 1941. Shelden, C. H.; Butt, H. R., and Woltman, H. W.: Vitamin E (Synthetic Alpha-Tocopherol) Therapy in Certain Neurological Disorders, Proc. Staff Meet., Mayo Clin. **15**:577 (Sept. 11) 1940. Doyle, A. M., and Merritt, H. H.: Vitamin Therapy of Diseases of the Neuromuscular Apparatus, Arch. Neurol. & Psychiat. **45**:672 (April) 1941. Denker, P. G., and Scheinman, L.: Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Alpha-Tocopherol), J. A. M. A. **116**:1893 (April 26) 1941. Ferrebee, J. W.; Klingman, W. O., and Frantz, A. M.: Vitamin E and Vitamin B_6: Clinical Experiences in the Treatment of Muscular Dystrophy and Amyotrophic Lateral Sclerosis, ibid. **116**:1895 (April 26) 1941.

13. The alpha tocopherol used in this study was supplied by Merck & Co., Inc., Rahway, N. J. Oral preparations of alpha tocopherol have been supplied by Winthrop Chemical Co., Inc., New York, as tofaxin and by Parke, Davis & Co., Detroit, as natural tocopherol.

RESULTS

In the group of patients with amyotrophic lateral sclerosis there were 6 in whom the disease was far advanced, 7 in whom it was moderately advanced and 6 in whom the disease was in an early stage. The majority were given alpha tocopherol in peanut oil by intramuscular injection, starting with 50 mg. twice weekly. The dose was later increased, and 1 of the patients received as much as 240 mg. daily over a period of four months, a total of 28,800 mg. In addition, all were given wheat germ oil and brewers' yeast. None showed any outstanding improvement. In 1 of the patients with far advanced disease there was no change; 1 showed slight subjective improvement with decrease in muscular fibrillations, but treatment was not continued; 3 had progression of symptoms during treatment, and 1 died. In the group with moderately advanced disease 2 patients noted a slight subjective increase in muscle power and many showed a moderate gain in weight (5 to 8 pounds [2.3 to 3.6 Kg.]). In a few instances the fibrillations were said to be less marked. Three patients showed no change, and in 2 the disability progressed. None presented objective evidence of increasing muscular power, and some showed objective evidence of progression of the disease in spite of subjective improvement. In the group with an early stage of the disease the response was similar; 1 patient who presented slight objective evidence of gain in muscular power early in the course of therapy later showed evidence of progression of the process. The patient with amyotrophic lateral sclerosis associated with syphilis noted slight decrease in fibrillations with some subjective gain in strength. In none of the patients with amyotrophic lateral sclerosis was there improvement in speech or deglutition; in none was there evidence of restoration of atrophic muscles, and in none was there change in the reflexes. It has been felt that in some of the patients, especially those with early disease, the progress of the disease may have been retarded, but this is only speculative, as it is well known that the course of this disease varies in individual persons and the patients the course of whose disease has been followed for a long enough period all showed progression. What appeared to be improvement early in the course of therapy did not continue in any case.

The response in the patients with progressive spinal muscular atrophy was very similar to that in patients with amyotrophic lateral sclerosis, which is to be expected, as these two conditions are closely related clinically and pathologically. Some patients noted a slight reduction in fibrillary tremors, more apparent subjectively than objectively, and 1 had a slight increase in strength. The symptoms progressed during the period of therapy in 2 cases.

The clinical trial was also ineffective in the patients with muscular dystrophy, and none showed evidence of response. The 2 patients

with poliomyelitis were treated in the paralytic stage. Both have shown some improvement, but the part the alpha tocopherol plays in this cannot be judged, as a certain amount of improvement always takes place in patients who survive. Both patients still have, however, outstanding residual parlyses, there has been no regeneration of atrophic muscles and in 1 of the patients the atrophy seems to have progressed.

Definite toxic reactions have been observed in only 2 patients. In 1 there developed a severe erysipeloid reaction at the site of injection, possibly an allergic response to the peanut oil which is used as a vehicle, and in the other, a generalized urticarial eruption, which disappeared when the preparation was discontinued but reappeared on readministration. There were questionable toxic reactions in 2 other patients. One patient who was pregnant showed signs of toxemia at the end of the second trimester and the preparation was discontinued, although it was not believed to be an etiologic factor in the toxemia; in the other patient hematuria developed during treatment.

Oral preparations of alpha tocopherol are being tried at present in the treatment of several patients with multiple sclerosis, the usual dose being 40 mg. three times a day, and wheat germ oil is being prescribed experimentally for all patients with multiple sclerosis who are seen in the clinics of the University Hospital. A few patients have reported some improvement following the use of alpha tocopherol, but in none has there been any outstanding change. Owing to the cyclic character of multiple sclerosis and its tendency to spontaneous remission, it is extremely difficult to evaluate the response of patients with this disease to any therapeutic regimen. One must be familiar with the clinical course over a period of years in each individual case before attempting to appraise any response to treatment.

CONCLUSIONS

No outstanding clinical response to the use of vitamin E and alpha tocopherol in the treatment of amyotrophic lateral sclerosis and progressive spinal muscular atrophy with progressive bulbar palsy has been demonstrated. The only changes of significance have been a slight decrease in the fibrillary tremors, oftentimes a feeling of well-being and a slight gain in weight and in some patients a subjective increase in muscular strength early in the course of therapy, which was not maintained. The progress of the disease may have been retarded or arrested in certain instances, but this is purely speculative, as the pathologic process proceeds with varying speed in different persons and the disease process progressed during the period of therapy in most instances. Large doses of alpha tocopherol (240 mg. daily) had no special advantage over smaller doses. Alpha tocopherol in large

doses was of no benefit in the treatment of far advanced muscular dystrophy. No definite acceleration of improvement was noted after its use in cases of poliomyelitis, and there was no regeneration of atrophic muscles. It is too early to judge the effects of the preparation in the treatment of multiple sclerosis.

Alpha tocopherol in its present form causes occasional toxic reactions, which should constitute a contraindication to the indiscriminate use of the drug.

The relation between the muscular and neuromuscular disorders produced in experimental animals by a diet deficient in vitamin E and the muscular atrophies and dystrophies occurring in human beings has not yet been satisfactorily explained. The experimental dystrophies, however, are primarily of muscular origin, and changes in the spinal cord, when they occur, are diffuse. The experimental dystrophies may resemble muscular dystrophies in human beings, but they are in no way related to amyotrophic lateral sclerosis, progressive spinal muscular atrophy and progressive bulbar palsy. The latter conditions are degenerative diseases, with involvement of the anterior horn cells in the spinal cord, the motor nuclei in the brain stem and the Betz cells in the motor cortex, and the atrophy in these diseases is secondary to the degeneration of the motor neurons. It is obvious that in these disorders regeneration of muscle can follow only regeneration of the motor neurons.

ABSTRACT OF DISCUSSION

Dr. F. P. Moersch, Rochester, Minn.: The justification for the enthusiasm in the treatment of certain neurologic disorders with vitamins is based on the assumption that one is dealing with a curable disease process. The results obtained by my associates and me in the treatment of the various muscular and neuromuscular disorders are quite in accord with those presented by Dr. DeJong. I have a few slides which will illustrate our results. There were 11 patients with amyotrophic lateral sclerosis, 9 with progressive muscular dystrophy and 6 with progressive muscular atrophy. Five of the patients with amyotrophic lateral sclerosis have died. At first we confined therapy to the use of wheat germ oil and alpha tocopherol. Later we also used brewers' yeast in tomato juice with pyridoxine, and finally we gave one group of patients alpha tocopherol alone. Our results have been discouraging, but, as all are aware, any one who treats conditions of this type accustoms himself to one discouraging experience after another. It would seem hardly proper to discard vitamin therapy entirely, but certainly help in combating these diseases must be sought elsewhere.

Dr. I. S. Wechsler, New York: I can multiply by three the number of failures reported by Drs. DeJong and Moersch. I may point out, however, that negative evidence is, as a rule, of no great significance. The more important question is whether in even a single case an invariably progressive and fatal disease has shown improvement. I am speaking not of cures but of arrest of progress and of reversal of one or more symptoms.

If what I say is true the treatment of degenerative diseases may be said to enter a new phase. The term "degenerative" is merely a convenient label and

describes certain pathologic changes. At best it is a challenge. Pathologically it describes an autopsy in vivo. More important is the fact that the pathologic changes in these neuromuscular disturbances bear resemblance to those seen in known avitaminoses.

Of the 60 patients whom I have seen and treated in the last two years, 50 failed to respond and only 10 showed varying degrees of improvement.

One patient who was almost entirely paralyzed and had an atrophic, fibrillating tongue walked out of the hospital; fibrillations and atrophy of the tongue and difficulty in swallowing are no longer present, and almost two years later, the patient is still alive and getting about the house, though with some difficulty. Another patient, who was expected by another neurologist to die within a few months, is still alive after a year and a half. A third patient, a young man who had atrophy of the hand, fibrillations and increased reflexes and who could not write for more than two or three minutes at a time, regained his power and has maintained it to date. And so on for the others, who showed varying degrees of regression.

Time alone will tell whether the treatment is of value, but one gain has already been made. My co-workers and I have devised a method of determining the tocopherol level in the blood. By means of photoelectric colorimetry we can tell how much of the vitamin E is absorbed and whether oral administration is as good as hypodermic medication. It seems to me that this is a real contribution. We shall continue our studies, and I shall continue to believe that negative reports have nowhere near the value of positive ones.

Dr. S. Bernard Wortis, New York: My associates and I, in the neurological department of Bellevue Hospital (Denker, P. G., and Scheinman, L.: Treatment of Amyotrophic Lateral Sclerosis with Vitamin E [Alpha-Tocopherol], J. A. M. A. **116**:1893 [April 26] 1941) and the Welfare Hospital for Chronic Diseases, under New York University Medical College, have frequently failed to observe any beneficial effects in cases of amyotrophic lateral sclerosis or muscular dystrophy in which treatment with vitamin E (alpha tocopherol) has been employed.

Dr. H. R. Viets, Boston: I must add a report from the Massachusetts General Hospital that conforms in practically every detail with Dr. DeJong's results. My associates and I have treated 21 patients, and, with 1 exception, the disease in all those patients has gone on to the usual fatal termination or has not shown any signs of improvement.

When Evans pointed out the changes in animals with vitamin E therapy, most felt, I think, that if vitamin E was going to be effective in man, it was more likely to be so in treatment of the dystrophies than of amytrophic lateral sclerosis or progressive muscular atrophy.

We began our studies with small doses of 10 to 15 mg. of alpha tocopherol per day and ultimately ran the amount up as high as 450 mg. a day in the case of 3 patients, who took that amount for six weeks. Now 1 of those patients, the last treated, has, rather to my surprise, not only failed to grow worse but actually improved. The diagnosis of that patient's condition was amyotrophic lateral sclerosis, as was that of the others, and it was not until we got our dosage up to over 150 mg. a day that improvement was shown. I wonder, therefore, if one does not owe a debt to Dr. Wechsler for his work, in spite of the many reports that have been published, and will continue to be published, in regard to the inefficiency of vitamin E in treatment of amyotrophic lateral sclerosis. Has he not shown, as has been done in neurology many times before, that amyotropic lateral sclerosis

is perhaps not a disease but a syndrome, and is it not possible that there are patients with the syndrome of amyotrophic lateral sclerosis who need vitamin E and will improve if they are so treated?

The change from the concept of a disease to that of a syndrome is surely not new; paralysis agitans is now considered no longer as a disease but as a syndrome, with many causes.

Probably the most important point of this discussion was that brought out by Dr. Wechsler, namely, that there is now a blood test for vitamin E and that with it one ought to be able to pick out of the 25, 50 or 100 patients with so-called amyotrophic lateral sclerosis those with low levels of vitamin E in the blood who should respond to this treatment.

DR. RUSSELL N. DEJONG, Ann Arbor, Mich.: I should state, in concluding the discussion, that even though many observers have had discouraging results in the treatment of amyotrophic lateral sclerosis and the muscular atrophies and dystrophies with vitamin E and alpha tocopherol, one should still have a ray of hope. The therapeutic measures that have been discussed today have apparently been of value in a few cases. The diseases under discussion are hopeless ones, and there has been no known treatment for them in the past. As a consequence, the fact that administration of vitamin E and alpha tocopherol seems to offer assistance in a few cases, even though only a small part of a large group, is justification for continuation of the therapy.

The other conclusion that would justify further investigation of the efficacy of these preparations is the possibility that one may be finding a new avenue of therapeutic approach. It took years to understand adequately the treatment of pellagra and some of the other vitamin deficiency diseases, and it may be that with more prolonged investigation, with a trial of vitamin E in combination with other vitamins, known or still unknown, one may eventually arrive at some method of giving assistance to patients suffering from these severe and incapacitating diseases.

Technical and Occasional Notes

A NEW APPROACH IN INDUCTION OF INFRAORBITAL NERVE BLOCK

PENN-GASKELL SKILLERN, M.D., SOUTH BEND, IND.

The use of local anesthesia in blocking a branch of the trigeminus nerve is frequent in office work, more so perhaps since the introduction of the electrosurgical unit. In induction of infraorbital nerve block I found myself dissatisfied with the usual method of introducing the needle through the cheek 1 cm. below the midpoint of the lower margin of the orbit: The foramen often had to be "fished for," and hematoma was liable to form. The oral approach is not desirable from the standpoint of surgical asepsis. One day I went lower—through the nasolabial sulcus—and found that the needle slipped into the foramen with the greatest of ease, without formation of hematoma.

TECHNIC

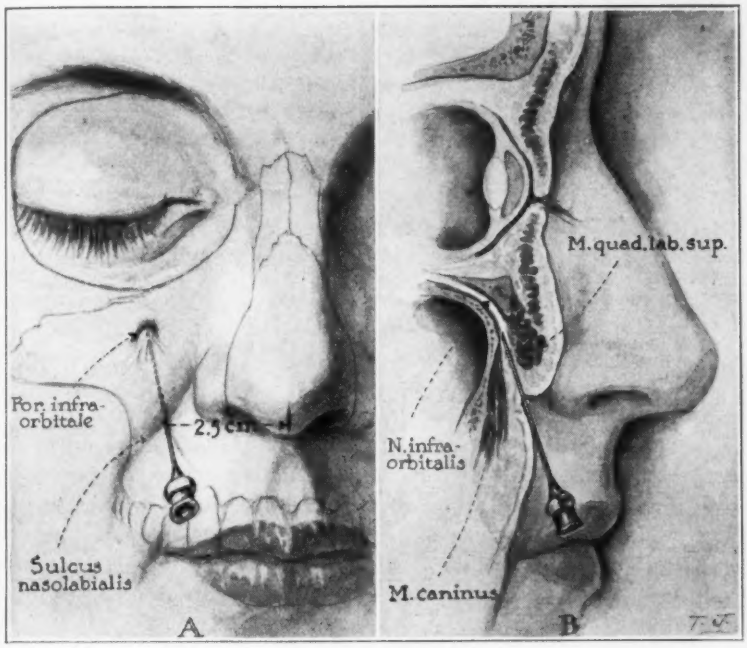
The landmarks (figure, *A*) to be observed in this approach are the anterior nasal spine (or the midline junction of the columella of nose and the philtrum of lip), the nasolabial furrow, the fold produced by the quadratus labii superioris muscle and the pupil directed forward.

The needle is introduced at a point on the nasolabial furrow where the latter is intersected by a line drawn from the anterior nasal spine lateralward for 2.5 cm. The needle is passed upward, backward and slightly outward, aiming at the pupil and, after traveling from 1 to 2 cm., is engaged by the foramen. In its passage the needle is depressed toward the foramen by the roll of the quadratus labii superioris muscle. This muscle arises from the maxilla just above the infraorbital foramen and therefore conceals the infraorbital nerve (and vessels). The caninus muscle arises from the canine fossa of the maxilla just below the infraorbital foramen and under cover of the quadratus labii superioris muscle. The needle, therefore, passes to the foramen between these two muscles.

The nasolabial furrow is a definite landmark and forms a depression between the roll of the orbicularis oris muscle, below, and the quadratus labii superioris muscle, above: The needle, therefore, traverses practically no muscle fibers but passes almost directly from the surface into the foramen, especially since it depresses the furrow toward the foramen during its passage (figure, *B*). During this maneuver the quadratus labii superioris muscle rolls upward and backward over the shaft of the needle, thereby guiding the needle to the foramen.

I use a B-D Firth-Brearley needle gage 26 and 3/8 inch long (0.95 cm.), which is so fine that its introduction is almost painless and which causes minimum laceration of the subcutaneous tissues.

1001-1002 Tower Bldg.



A shows landmarks and the direction taken by the needle.

B shows the needle passing between the quadratus labii superioris muscle, above, and the caninus muscle, below. Note how the former muscle depresses the needle toward the foramen and how the nasolabial furrow rides upward with the needle, thus shortening the distance from the surface to the foramen. Note, too, that the needle passes upward parallel to the infraorbital canal instead of perpendicular to it, as in the older method.

News and Comment

THE AMERICAN BOARD OF NEUROLOGICAL SURGERY

At a meeting of the American Board of Neurological Surgery held in St. Louis, Oct. 31 and Nov. 1, 1941, the following diplomates were certified:

George S. Baker, Rochester, Minn.; Roland T. Bellows, Charlotte, N. C.; Spencer Braden, Cleveland; Howard A. Brown, San Francisco; Harold F. Buchstein, Minneapolis; Arthur D. Ecker, Syracuse, N. Y.; James Greenwood Jr., Houston, Texas; Lester B. Lawrence, Oakland, Calif.; Richard U. Light, Kalamazoo, Mich.; William Rutledge Lipscomb, Denver; Augustus McCravey, Fort Bragg, N. C.; John M. Meredith, Richmond, Va.; Lester A. Mount, New York; Frederick L. Reichert, San Francisco; Robert C. L. Robertson, Houston, Texas; Adrien Verbrugghen, Chicago; James W. Watts, Washington, D. C.; Walter R. Wegner, Boston, and Wilfrid D. Wingebach, New York.

ANNOUNCEMENT OF FELLOWSHIPS: THE NATIONAL COMMITTEE FOR MENTAL HYGIENE

A limited number of fellowships are being offered for training in extramural and child psychiatry. Initial selection for these fellowships is to be made by the National Committee for Mental Hygiene, by whom eligible applicants are to be recommended for appointment in selected training clinics. These fellows will spend one or two years in a selected clinic, the term and plan of the fellowship to be determined by the peculiar needs of the applicant. The training is pursued according to a definite plan related to the probable future functions of these fellows. Candidates for fellowship award should have had at least a general internship and two years of psychiatry in an approved mental disease hospital service, in addition to other qualities fitting them for extramural service. Since this provision of training fellowships comes in response to a definite paucity of personnel in this field, peculiarities of the demand are considered in making appointments. The stipends vary slightly with the location and the status of the fellow but in general range between $2,000 and $2,600.

Requests for further information about these fellowships, and applications therefor, should be addressed to Dr. Milton E. Kirkpatrick, the National Committee for Mental Hygiene, 1790 Broadway, New York.

PENNSYLVANIA PSYCHIATRIC SOCIETY

William C. Porter, M.D., Lieutenant Colonel, Medical Corps, United States Army, Chief of Neuropsychiatric Section, Walter Reed General Hospital, Washington, D. C., spoke on "Psychiatry and the National Defense" at the third annual dinner meeting of the Pennsylvania Psychiatric Society at the Bellevue-Stratford Hotel, Philadelphia, the evening of Oct. 9, 1941.

Henry I. Klopp, M.D., president of the society, superintendant, Allentown State Hospital, presided and delivered the presidential address.

Edward A. Strecker, M.D., chairman of the Department of Psychiatry, University of Pennsylvania School of Medicine, introduced Colonel Porter.

Officers for the coming year, 1941-1942, are as follows:

President: Baldwin L. Keyes, M.D., Philadelphia, professor of psychiatry, Jefferson Medical College.

President Elect: George J. Wright, M.D., Pittsburgh, professor of neurology, University of Pittsburgh School of Medicine.

Secretary-Treasurer: LeRoy M. A. Maeder, M.D., Philadelphia.

Councillors: Ralph L. Hill, M.D., Wernersville, Pa.; Henry I. Klopp, M.D., Allentown, Pa.; Arthur P. Noyes, M.D., Norristown, Pa.; William W. Richardson, M.D., Mercer, Pa.; Thomas A. Rutherford, M.D., Waymart, Pa.; George W. Smeltz, M.D., Pittsburgh, and Lauren H. Smith, M.D., Philadelphia.

Auditors: Robert H. Israel, M.D., Warren, Pa.; Howard K. Petry, M.D., Harrisburg, and Charles A. Zeller, M.D., Philadelphia.

Abstracts from Current Literature

Physiology and Biochemistry

DEVELOPMENT OF SWIMMING AND RIGHTING REFLEXES IN FROG (RANA GUENTHERI): EFFECTS THEREON OF TRANSECTION OF CENTRAL NERVOUS SYSTEM BEFORE HATCHING. GING-HSI WANG and TSE-WEI LU, J. Neurophysiol. **4**:137 (March) 1941.

The development of aquatic locomotion in Rana güntheri passes through the following stages: (1) the nonmotile stage, (2) the flexure stage, (3) the stage of the S reaction, (4) the stage of translatory movements of the body, (5) the stage of the control of the directions of swimming and (6) the stage of the maintenance of normal orientation to the earth's gravitation field during motion and rest.

The last two stages are easily affected by transverse lesions made in the embryo on the central nervous system. The severance of the spinal cord arrests the development of swimming at stage 4, and after the transection of the brain at the caudal border of the mesencephalon the development of aquatic locomotion does not reach beyond stage 5. The removal of the forebrain and the interbrain, or of the telencephalon alone, has no effect whatever on the ontogeny of swimming.

The righting reflexes appear in stage 4 of the development of swimming, and the transection of the central nervous system at any level caudad to the rostral border of the hindbrain prevents the larvae operated on from acquiring these postural reflexes. With tadpoles of 6 mm. body length which have not yet developed the righting reflexes, the removal of both labyrinths produced its usual effect on locomotion in making them lose the control of the direction of swimming.

The transection of the spinal cord induces in the larvae an exaggeration of the flexor reflexes of the tail and consequently causes it to be permanently ventroflexed, while decerebration produces an accentuation of the extensor reflexes of the tail and consequently makes it permanently extended. Such effects are absent after the transection of the central nervous system rostrad to the rostral border of the midbrain.

The normal and mesencephalic larvae can recover from the effects of double labyrinthectomy if there is no concomitant injury to the hindbrain. On the transection of the brain at the caudal boundary of the mesencephalon the symptoms of the extirpation of both labyrinths immediately return. The decerebrated tadpoles do not recover from the effects of double labyrinthectomy.

The spinal, decerebrated and mesencephalic tadpoles are as spontaneously active as the diencephalic and normal ones. This is entirely contrary to the results with adult frogs.

ALPERS, Philadelphia.

TRANSMISSION OF IMPULSES THROUGH THE BURDACH NUCLEUS. P. O. THERMAN, J. Neurophysiol. **4**:153 (March) 1941.

After a single shock applied to a nerve of the forelimb there passes through the dorsal column to the nucleus of Burdach a volley of primary impulses, succeeded after about three milliseconds by the dorsal column relay of Hursh. These impulses produce in the nucleus a postprimary negative potential lasting about five milliseconds. During the course of this potential impulses are discharged into the lemniscus.

Conditioned transmission through the nucleus has the following properties: The refractory period at the synapse is not longer than that of the primary axons. Transmission after the second of two volleys at intervals of less than five milliseconds is limited to a short burst of spikes (lasting about 1 millisecond) following

the second primary volley by a synapse time of six-tenths millisecond. Addition of the later, more inhibitable, portion of the transmitted impulses starts at intervals of five milliseconds, and restoration is complete in fifteen to fifty milliseconds. Thus the transmission of tetanus through the nucleus is essentially one to one conduction between primary neurons and neurons of the lemniscus fibers.

A positive wave lasting about one hundred milliseconds, recorded at the surface of the nucleus, is correlated with activity in the underlying reticular substance.

ALPERS, Philadelphia.

INFLUENCE OF DISCHARGE OF MOTONEURONS UPON EXCITATION OF NEIGHBORING MOTONEURONS. BIRDSEY RENSHAW, J. Neurophysiol. **4**:167 (March) 1941.

An antidromic volley in a group of motoneurons produces a small centrifugal discharge from the spinal cord into some of the motor axons which carry the antidromic impulses. No centrifugal impulses appear in the axons of other motoneurons. The centrifugal impulses appear to be repetitive discharges set up at some central portion of the motoneurons, rather than reflex discharges synaptically excited through recurrent collaterals.

Antidromic volleys do, however, condition synaptically excited discharges of other motor cells. Inhibition typically occurs if the tested and the conditioning motor nerves are branches to the same muscle or muscle group. The response deficit then reaches its maximum when the conditioning antidromic volley arrives at the cord two to four milliseconds before the tested motor discharges are set up. The amount of inhibition then gradually declines. It disappears when the antidromic volley precedes the tested discharge by about fifty milliseconds.

A particularly significant feature of the inhibition is its early onset. A response deficit is present if the antidromic volley reaches the ventral horn simultaneously with the testing impulses which fire the tested motoneurons after a single synaptic delay. This finding cannot be explained on the assumption that the only effect which an active neuron exerts on other neurons is the detonator excitation produced by the arrival of impulses at synapses.

Conditioning also occurs when the antidromic volleys and the tested motor impulses occupy the nerves to different muscles or muscle groups. Both facilitation and inhibition have been observed. Facilitation usually follows a brief initial period of inhibition. Maximal facilitation is attained when the conditioning antidromic volley precedes the tested discharge by about twenty-five to thirty milliseconds. It then declines and disappears only when the interval between conditioning and tested volleys exceeds one hundred milliseconds.

ALPERS, Philadelphia.

FUNCTIONAL ANATOMY OF BRACHIUM PONTI. R. S. TURNER and W. J. GERMAN, J. Neurophysiol. **4**:196 (March) 1941.

The effects of section of the brachium pontis were studied in 3 monkeys (2 mangabeys and 1 Java monkey) over periods of five to twenty months. The investigation included psychobiologic tests (problem boxes) to which the animals were previously trained and determinations of cerebellar function, posture, gait, equilibrium, muscle tone and personality characteristics. The operative lesions and their resultant degenerations were verified histologically. The results may be summarized as follows: Neither the execution of learned behavior problems nor the retention of their solutions was significantly affected by unilateral or bilateral section of the brachium pontis. Unilateral section of the brachium pontis was followed by curvature of the head and spine, spiraling and circus movements toward the side of the lesion; awkwardness of the lower extremities in locomotion, with incoordination between the hindlimbs and the forelimbs, and slight hypotonia of both lower extremities. These symptoms disappeared within three to four weeks. A decrement in activity sometimes endured somewhat longer. Transient

dysmetria and nystagmus were present for a few days after operation. No tremors in either voluntary or associated movements were noted at any time. Bilateral section of the brachium pontis resulted in the same symptoms as the unilateral operation, but enduring awkwardness of gait and diminished general activity were present. The hand-eye coordination was reduced 20 to 30 per cent below the preoperative normal. The bilateral operation was followed by a progressive symptom complex, consisting of incoordination between the lower and the upper extremities in locomotion, disequilibrium and sluggishness of general behavior.

The following implications may be drawn from the results of this study: The corticopontocerebellar system is not necessary for the performance of precise manual functions or learned behavior. The complete compensation which occurs after unilateral lesions indicates that the corticopontocerebellar system is capable of bilateral function. Functionally, the corticopontocerebellar system seems to be necessary for the coordinated activity of large movement complexes, such as that of the lower and the upper extremities in locomotion. ALPERS, Philadelphia.

VEGETATIVE REACTIONS IN HUMAN SUBJECTS AND THEIR DEPENDENCE ON THE TYPE OF STIMULUS. B. JÜRGENS, Arch. f. Psychiat. **111**:88 (Jan.) 1940.

Jürgens conducted his investigations on 20 normal subjects and on 30 patients suffering from various organic disturbances, catatonic stupor or epilepsy. The studies consisted in recording vasomotor reactions by means of the finger plethysmograph and the galvanic skin reflex. The stimuli used were those of pain, temperature and fright. The relations to respiration, the electrocardiogram and the electroencephalogram were also recorded. It was found that the vasomotor reactions and the galvanic skin reflex were definitely related to the quality of the stimulus. Pain and fright stimuli produced an intense galvanic skin reflex accompanied by a vasomotor reaction. Low temperature, on the other hand, had very little effect on the galvanic skin reflex. These specific differentiations could be varied, however, by changes in the psychic and emotional factors. A difference was found in the latent period of the two reactions. The latent period of the vasomotor response was much longer than that of the galvanic skin reflex. Similar differences in latency were found in responses to other stimuli. After the stimulations there was a consistent change in pulse rate, with alternating acceleration and retardation. These responses, again, varied with the qualities of the stimuli. In pathologic subjects the reactions deviated from normal. In some of them the deviations were directly referable to interference with the receptor mechanisms. In others they seemed to be caused by pathologic conditions in the central mechanisms or in the peripheral effectors. Lasting changes were found to follow anatomic lesions of the peripheral nerves, the cord or the brain stem. With tumor of the hypothalamus no such changes were recorded. In catatonic stupor the intensity of the reactions was normal, but there was a pathologic increase in the latent period of the vasomotor reactions.

MALAMUD, Worcester, Mass.

LOW INTRACRANIAL PRESSURE AS A SYMPTOM OF VEGETATIVE HYPEREXCITABILITY. WILHELM GELLER, Deutsche Ztschr. f. Nervenh. **151**:91, 1940.

For this investigation, the spinal fluid pressure was measured by cisternal puncture with the patient in the recumbent position. The author considers pressures from 80 to 180 mm. of water as within the normal range. The material comprises 3,686 cases of cisternal puncture. Of them, the initial pressures were below 50 mm. in 89 cases, i. e., in 2.5 per cent. The lowest pressures were zero in a woman suffering from cerebrospinal syphilis and 5 mm. in a man with multiple sclerosis. In patients with low intracranial pressure the final pressure was only slightly lower than the initial pressure. The majority of the 89 patients with low pressure were those with injuries to the head, multiple sclerosis and psycho-

pathic states. Of the total number of patients examined, those with paralysis agitans, psychopathy and syringomyelia had the highest incidence of low intracranial pressure (20, 14 and 10 per cent, respectively). Almost all the patients with low intracranial pressures had signs and symptoms of hyperirritability of the autonomic nervous system, expressed by hyperhidrosis, flushing and dizziness, with optic scintillations and headaches. Injections of dextrose did not improve the condition. Men complained of hypersusceptibility to alcohol and nicotine. In addition, almost all the patients presented low blood pressures. Geller was unable to decide whether the low pressures were caused by constitutional abnormalities of the autonomic nervous system or whether the disease of the central nervous system in itself produced disturbance of the equilibrium of the autonomic system. In acute conditions an attempt should be made to relieve the disturbance by regulating the water metabolism of the whole body.

ADLER, Boston.

DEVELOPMENT OF GAIT. W. BIRKMAYER and H. GOLL, Deutsche Ztschr. f. Nervenh. **151**:237, 1940.

Birkmayer and Goll analyzed the gait of children of different ages by means of moving pictures. Special interest was directed to the development of gait in the growing child. No general mathematical law could be found, and some statistical results seemed to be contradictory. The authors explain this by referring to the irregularity of the gait of the young child, in whom the various phases of gait change in time and quality. The duration of standing between single steps is prolonged, the supporting area is larger and the center of gravity falls within the supporting area. The head and trunk are shifted forward. This causes the young child to have difficulties in stopping himself when he starts to walk. The forward shift of the trunk causes the legs to hurry after the trunk in order that the child may avoid falling. The duration and length of steps, as well as the swinging time of the legs, increase in the growing child. The supporting surface decreases, and the center of gravity, in several phases of gait, falls outside of the supporting area as the child grows.

ADLER, Boston.

Diseases of the Brain

PRIMARY PITUITARY ADENOMA AND THE SYNDROME OF THE CAVERNOUS SINUS. LAURENCE M. WEINBERGER, FRANCIS HEED ADLER and FRANCIS C. GRANT, Arch. Ophth. **24**:1197 (Dec.) 1940.

Of the classic triad of signs, the chiasmal syndrome, constitutional dyspituitarism and roentgen evidence of hypophysial disease, the first-mentioned has played the largest role in the recognition of pituitary adenoma. Indeed, the preeminence of the visual component in the semiology of pituitary adenoma led Henderson, who recently published a critical review of Cushing's series of 338 cases, to declare: "It is exceptional for a chromophobe adenoma to be diagnosed or even suspected before it is sufficiently large to implicate the visual pathways. . . . operation would hardly be justified before vision is affected."

The occurrence of paralysis of the ocular nerves as an early, or in some cases the first, evidence of pituitary adenoma seems to have been first pointed out by Foix. He described a case in which a pituitary tumor first evidenced itself by severe pain in the region of the ophthalmic division of the fifth nerve and was associated with rapidly progressive unilateral paralysis of the third nerve, followed in turn by paralysis of the fourth and sixth nerves.

This accompanying paralysis of the oculomotor nerves as a syndrome of primary pituitary adenoma seems to have been neglected. Of 169 cases of verified pituitary adenoma, the authors were able to selected 14 cases in which unusual neuro-ophthalmic pictures permitted them to divide these, on the basis of a cavernous sinus syndrome, into three subgroups: (1) those in which the disturbances referable

to the ocular and trigeminal nerves comprised the exclusive neurologic picture; (2) those in which the symptoms referable to the ocular and trigeminal nerves dominated the clinical picture but in which there were some evidences of implication of the optic chiasm, and (3) those in which the disturbances referable to the ocular and trigeminal nerves were an important part of the clinical symptoms but in which there were unequivocal visual field defects indicating an intrasellar lesion.

The disturbances referable to the ocular and trigeminal nerves in these cases were accounted for by the implication of the cavernous sinus. It was shown that occasionally pituitary adenomas grow laterally and that this mode of growth may produce the clinical picture of a lesion in the sphenoid fissure rather than the classic chiasmal syndrome.

Of special importance in the presentation was the analysis of the anatomic basis of the syndrome. The essential etiologic factors naturally require that the pituitary adenoma grow out of the sella laterally. SPAETH, Philadelphia.

ETHER CONVULSIONS. HAMILTON BAILEY, Brit. M. J. **2**:222 (Aug. 17) 1940.

Bailey describes several cases of fatal convulsions following ether anesthesia and 2 other cases in which the convulsions were treated successfully. A capsule of calcium gluconate administered intravenously in the early stage relieved the twitchings in 1 case but was ineffective in the other. In spite of the generally accepted contraindications, evipal sodium (a sodium salt of n-methyl-C-C-cylcohexamethyl barbituric acid) was then given, with recovery. It is frequently stated that ether convulsions have some relation to hot weather, but Bailey observed 2 cases in unusually cold weather. He suggests therefore that the convulsions may be due to overheating of the water which vaporizes the ether.

ECHOLS, New Orleans.

CEREBRAL LESIONS FOLLOWING CONVULSION THERAPY FOR SCHIZOPHRENIA. JAN CAMMERMEYER, J. belge de neurol. et de psychiat. **40**:169 (April) 1940.

Cammermeyer concludes, after studying pathologic changes in the brain following metrazol and insulin therapy, that both forms of treatment may produce serious alterations in structure of the brain. The lesions brought about by insulin therapy resemble those produced by circulatory disturbances, although in many cases in which death followed the use of large doses of insulin there were no serious parenchymal or vascular lesions. Insulin hypoglycemia produces anoxia, and death is probably caused by extensive necrosis of cerebral tissue. After metrazol therapy there may be widespread cortical changes, with complete disappearance of neurons. The pathologic picture more closely resembles that seen in toxic processes.

From the pathoanatomic point of view, Cammermeyer is not able to state a preference for either insulin or metrazol therapy. This preference must be decided on the basis of clinical results and statistical data. It is not possible to state whether the cerebral changes following insulin therapy or those following metrazol convulsions are more severe. DE JONG, Ann Arbor, Mich.

CEREBRAL FAT EMBOLISM. ALEXANDER SILVERSTEIN and FRANK KONZELMAN, Confinia neurol. **3**:129, 1940.

Silverstein and Konzelman report the case of a youth aged 19 in whom convulsions and then extensor rigidity of the entire body developed a few hours after an injury in which he received contusions over both legs. Two days later petechial hemorrhages appeared over the chest and in the conjunctivas; the following day pneumonia developed, and there was projectile vomiting of coffee ground material; the next day he died. Unconsciousness, persistent hiccup, dyspnea and a high fever were present during the entire illness. Postmortem examination showed,

in addition to bronchopneumonia, marked cerebral changes with edema, petechial hemorrhages and multiple areas of coagulation necrosis. Fat stains showed fat emboli in the capillaries and the smaller blood vessels, particularly in the necrotic areas.

The authors consider that cerebral fat embolism is a well established pathologic syndrome which may follow jarring of the skeleton, orthopedic procedures and surgical operations on the viscera, as well as fractures of the long bones. They state that a study of cerebral fat embolism may shed additional light on some of the unexpected fatalities following trauma to the head and on the neurologic manifestations following cranial and spinal operations.

DE JONG, Ann Arbor, Mich.

STEWART-MOREL SYNDROME (HYPEROSTOSIS FRONTALIS INTERNA): REPORT OF FOUR CASES. J. O. TRELLES and M. MENDEZ, Rev. de neuro-psiquiat. **2**:342 (Sept.) 1939.

Trelles and Mendez report 4 cases of hyperostosis frontalis interna. The condition in these cases seemed in accord, for the most part, with the classic descriptions of the disease. All the patients were women; 2 had passed 60, 1 was 42 and 1 was 32 years of age. The case of the last patient is evidence against the opinion expressed by Henschen that the disease is an accompaniment of advanced years. All 4 patients showed obesity, which affected chiefly the trunk and the proximal portions of the extremities. In 1 instance obesity was replaced in the final period of the disease by extreme thinness. The authors believe that the obesity is due to disturbance in function of the pituitary gland and that near the terminal stage of the disease a more profound disturbance may in some cases bring about the terminal thinness.

Mental disturbances were fairly definite in 2 of the younger patients and were pronounced in 1 of the older. They showed no particular characteristic. Three of the patients presented classic changes in the internal part of the frontal bone, such as were described by Morel, 2 of whom showed increased pneumatization of the paranasal sinuses. In the fourth patient the hyperostoses extended beyond the limits of the frontal bone and involved the parietal bone, which was markedly thickened from the sagittal suture to the temporoparietal suture.

Epileptic crises were noted in 3 of the patients. Two had headache. One patient presented sensory changes, 1 scintillating scotomas and 1 visual disturbances, the last symptom being due probably to coexistent syphilis. One patient showed weakness of the left upper extremity. Examination of the blood and urine revealed nothing abnormal.

The authors believe that the only characteristic disturbance in cases of this disease is the hyperostosis. Obesity, usually present, presents a number of variations. All of the other manifestations, including the mental disturbances, are seen in varied forms.

NORCROSS, Toledo, Ohio.

AN ISOLATED LESION OF THE LOWER OLIVE IN A CASE OF MYOCLONUS EPILEPSY. OSCAR AMMERMANN, Arch. f. Psychiat. **111**:213 (March) 1940.

Ammermann reports a case of myoclonus epilepsy which started at the age of 9 years and, after a chronic course, led to increasingly frequent attacks and death. The anatomic examination showed as the only lesion a bilateral process in both lower olives. Such an isolated lesion has been reported previously in cases of this disease. Other reports have emphasized an extension of the changes to the dentate nucleus. The fact has been stressed that although these two centers are not connected by tracts, they nevertheless show marked similarities in structure and frequently are affected simultaneously. The olive-dentate system is particularly frequently involved in cases of myoclonia of the soft palate, and it is argued from this that the olives play a special role in disease of the extrapyramidal system.

MALAMUD, Worcester, Mass.

PARKINSON'S DISEASE (PARALYSIS AGITANS) AND POSTENCEPHALITIC PARKINSONISM. RUDOLPH KLAUE, Arch. f. Psychiat. **111**:251 (March) 1940.

The present investigation was carried out on 100 patients, the brains of 74 of whom were examined histologically. The patients are divided into three groups, the first consisting of 32 patients with paralysis agitans, the second of 28 patients with postencephalitic parkinsonism and the third of 14 patients whose conditions are designated as atypical, having characteristics of both diseases. Clinically, the only differentiating points between the groups seem to be quantititive variations. The group with postencephalitic parkinsonism, as contrasted with the group with paralysis agitans, shows less pill-rolling tremor, more frequent occurrence of disturbances of the ocular muscles and nystagmus, more intense disturbances of speech, more frequent increase in salivation and polyuria, less frequent signs of dementia or hallucinations and a history of encephalitis. It is emphasized that the pathologic changes in the striatum and pallidum, as opposed to those in the substantia nigra, are not necessarily restricted to Parkinson's disease, since they may also occur in normal old people. As contrasted with this, the black zone of the substantia nigra is not affected in nonparkinsonian patients. A similar change is also recorded in the locus caeruleus. In both these structures the changes consist in degeneration and dropping out of cells and in glial reactions. These are most marked in the caudal part of the substantia nigra. In postencephalitic parkinsonism the changes are much more restricted to the substantia nigra and, unlike those in paralysis agitans, are not isolated, but diffuse. These differences, however, are only quantitative, the changes in postencephalitic parkinsonism being more intense.

The disturbances in architecture, regarded by some as a differentiating point, are not seen in most cases. The author concludes that it is not justifiable to regard the clinical differences between the two types as dependent on variations in localization but that both clinically and pathologically the differences are only quantitative.

MALAMUD, Worcester, Mass.

THE EPILEPTIC SYMPTOM COMPLEX, ASSOCIATED WITH TUMOR OF THE FRONTAL LOBE, WITHOUT CONSIDERATION OF THE RELATION TO AREA 4. GEORGE DESTUNIS, Arch. f. Psychiat. **111**:421 (May) 1940.

Of 261 verified tumors of the brain, 103 were associated with a history of epilepsy, and of these about a third were tumors of the frontal lobe. Destunis concludes that epileptic convulsions, in cases of tumor of the brain, occur most frequently with tumors of the frontal lobe. They are more likely to occur if the lesion is on the left side. The incidence is particularly high in persons of the fourth to the sixth decade of life. In about half the cases the convulsion was the first symptom of the disease. The types of epilepsy vary a great deal, especially in cases of intracerebral tumor. Localizable phenomena were not frequent. A number of areas combine in producing the attack, thus leading to complicated, atypical phenomena. The fact that there is usually no distinct aura and that the character of the convulsion is not at all clearly related to the area involved makes it difficult to use the convulsions in an attempt to localize the lesion. Fainting spells, myoclonus and akinetic and psychogenic convulsions were rarely observed. The generalized character of the convulsion, its complexity and the unconsciousness accompanying it must be regarded as related to the anatomic and physiologic characteristics of this part of the brain. Of the accompanying symptoms, the most frequent are disturbances of the cranial nerves (especially the seventh), symptoms referable to the pyramidal tract, disturbances of equilibrium and coordination, mental symptoms, speech disturbances and extrapyramidal manifestations.

MALAMUD, Worcester, Mass.

EPILEPSY AND MULTIPLE SCLEROSIS. G. E. STÖRRING, Arch. f. Psychiat. **112**:45 (Aug.) 1940.

On the basis of a series of cases of multiple sclerosis in which epileptic convulsions were noted, Störring discusses the differential diagnosis of so-called genuine epilepsy and the symptomatic epilepsy of multiple sclerosis. Epileptic convulsions do not occur frequently in cases of multiple sclerosis, and when present they manifest themselves early in the disease. Of 205 cases of multiple sclerosis, epileptic symptoms were present in 13. The cases fall into two groups. The first consists of cases in which the exogenous character of the convulsion is clear and focal symptoms characteristic of multiple sclerosis are found. The convulsions in such cases are not uniform and show peculiarities which differentiate them from the genuine epileptic seizures. They occur so early in the disease that they may precede the clearly demonstrable neurologic signs of the disease. In the second group belong the cases in which it is impossible at first to differentiate the convulsion from that of genuine epilepsy. Even the occurrence of a twilight state following the convulsion has been noticed. Occasionally examinations of the cerebrospinal fluid and pneumoencephalographic studies are helpful. Most important is the fact that no matter how similar the convulsion itself may be to that of genuine epilepsy, one never finds the personality changes and characteristics which are peculiar to idiopathic epilepsy. Petit mal attacks are extremely rare in these cases. Hereditary tainting was not found in any of the cases in either group.

MALUMUD, Worcester, Mass.

CASE OF RIGHT-SIDED HEMIPLEGIA, MOTOR APHASIA, AGRAPHIA, ANOSOGNOSIA AND FANTOM EXPERIENCES IN THE PARALYZED ARM, WITH SPECIAL CONSIDERATION OF THE RESTITUTION OF FUNCTION. G. ZILLIG, Arch. f. Psychiat. **112**:110 (Aug.) 1940.

Zillig reports observations in a case of cerebral embolism due to mitral stenosis in which were found right hemiplegia, aphasia, agraphia, anosognosia and fantom experiences in the paralyzed (right) arm. Restitution of the various functions was observed during convalescence. Of particular interest were the manifestations of return of the function of writing. The patient, who first acquired the ability to write in German script and only afterward learned to use Latin characters, was for some time after the occurrence of the lesion able to write in German but not in Latin characters. Of further interest was the fact that at a certain stage of the convalescence, when the arm was still paralyzed, there was a period during which, in the presence of anosognosia, the patient experienced a fantom paralyzed limb.

MALAMUD, Worcester, Mass.

Vegetative and Endocrine Systems

CORRELATION OF PHYSIOLOGICAL AND CYTOLOGICAL CHANGES IN THE NEUROHYPOPHYSIS OF RATS WITH EXPERIMENTAL DIABETES INSIPIDUS. I. GERSH and C. MCC. BROOKS, Endocrinology **28**:6 (Jan.) 1941.

Gersh and Brooks describe the results of various operative lesions in the hypothalamic region in 29 rats. The nature of the lesions and the disturbances in water intake and output were correlated with the cytologic changes in the parenchymatous cells of the neurohypophysis. In 5 control rats with no disturbance of water balance, the lesions were in the brain stem posterior to the median eminence or anterior to the optic chiasm, and the cells of the neurohypophysis were normal. In 8 hypophysectomized rats, there occurred only temporary postoperative polyuria and polydipsia, and the parenchymatous cells in the remaining portion of the neurohypophysis fell within the normal range, or slightly above it, in size, number and

distribution. Of the 16 rats in which diabetes insipidus, of varying degree and permanence, developed, the physiologic disturbance was correlated with the degree of damage to the supraopticohypophysial system. In the unquestionably diabetic animals, the lesions destroyed the greater part of the innervation of the neurohypophysis by destruction of the stalk or by serious injury to nerve tissue between the median eminence and the supraoptic nuclei. The denervated parenchymatous cells became atrophic. Compensatory hypertrophy of less differentiated cells sometimes occurred. These, in turn, might undergo atrophy through exhaustion.

PALMER, Philadelphia.

LAURENCE-MOON-BIEDL SYNDROME, WITH TETANY. FRANCIS D'ABREU and DAVID FERRIMAN, Brit. M. J. **1**:157 (Feb. 1) 1941.

D'Abreu and Ferriman describe the case of a 25 year old woman which they consider to be an instance of the Laurence-Moon-Biedl syndrome without polydactyly or mental deficiency. Although obesity was present at one time, the patient was of normal weight when seen by the authors. Characteristic of the syndrome were a recessive mode of inheritance, menstrual disturbance and attacks of tetany. Improvement in the patient's condition followed treatment with 20 cc. of calcium lactate and 50,000 international units of vitamin D daily. Green explained the tetany in this disorder as "a consequence of the body's failure to adapt itself, as yet, to the relatively low calcium level."

ECHOLS, New Orleans.

ADRENAL INSUFFICIENCY IN EPILEPSY. E. CANTILO, Prensa méd. argent. **27**:2641 (Dec. 18) 1940.

Cantilo states that chronic adrenal insufficiency in the absence of any other pathologic factor may be the cause of epileptic crises of the type of essential epilepsy or its equivalents. The condition is symptomatic for adrenal insufficiency and can be controlled by proper endocrine therapy without bromides and barbiturates. Patients with this type of epilepsy have an asthenic body build, hyperpigmented skin, depressive temperament, hypoglycemia during fasting and diminished insulin tolerance. Glycemia and insulin tolerance return to normal values if the epileptic crises are controlled by endocrine therapy. The author reports satisfactory results in 3 cases from administration of endocrine extracts in daily doses of 0.5 Gm. of extract of the anterior lobe of the hypophysis, 0.25 Gm. of extract of whole adrenal gland and 0.1 Gm. of extract of the thyroid. The extracts were administered by mouth. The patients received chorionic gonadotropin (pregnyl) in doses of 1 cc. containing 500 units of the principle every other day for the first two months of the treatment. In cases reported by the author, glycemia and insulin tolerance returned to normal values and the epileptic crises were controlled up to the present, for more than one year, without administering any other drug. The author believes that this type of epileptic crises is due to sudden lowering of glycemia, which is preventable by endocrine therapy.

J. A. M. A.

SIMMONDS' SYNDROME. E. MOGENSEN, Acta med. Scandinav. **105**:360 (Nov. 14) 1940.

Mogensen suggests that Simmonds' disease may be caused by any process which destroys the anterior lobe of the pituitary and that the fundamental morbid process is so variable as to suggest the propriety of the term Simmonds' syndrome. The syndrome is a chronic, progressive disorder due to failing of the endocrine function of the anterior lobe of the pituitary and is characterized by the deficiency symptoms produced thereby. Cachexia is a late phase of the disease and by no means a necessary symptom. If the diagnosis is not made until cachexia appears, it is a late one. The pathologic changes, besides those already mentioned, are atrophy of

the pituitary body, skin, sexual glands, thyroid, parathyroids and adrenals. In advanced stages the internal organs are atrophied. The author believes that the main symptoms of the disease may be ascribed to a decreased secretion of the hormones of the anterior lobe; the loss of weight and the splanchnomicria to lack of the growth hormone; the genital atrophy, loss of hair and presenility to lack of gonadotropic hormones, and hypoglycemia to lack of the diabetogenic hormone. It is possible that the decreased basal metabolism is due to a decrease of the thyrotropic hormone, but it is also possible that the symptom is due to a decrease in the specific dynamic value of the proteins (Plaut, and Goldzieher and Gordon). The reduced blood pressure may possibly be due to adrenal insufficiency. The anemia is perhaps caused by the lack of hemopoietic pituitary hormone, or possibly by an existing achlorhydria. Many symptoms of Simmonds' syndrome cannot as yet be explained satisfactorily, as knowledge of the functions of the pituitary is still meager. In the differential diagnosis the conditions that should be considered are pluriglandular insufficiency, myxedema, Addison's disease, eunuchoidism, forms of emaciation terminating in cachexia and especially anorexia nervosa. In general, anorexia nervosa has a far more benign course than has Simmonds' disease, and many patients with this disturbance have recovered within a short time under various forms of treatment. There are numerous reports of the successful treatment of the disease in cases of what was obviously anorexia nervosa. Of the many types of treatment used, the most promising results have been obtained with a preparation containing the gonadotropic substance from the urine of pregnant women. The author has produced and maintained pronounced improvement of the general condition and symptoms of endocrine deficiency in 2 male patients with Simmonds' disease by intense treatment with chorionic gonadotropin. In a third patient, a woman, this treatment failed, probably because the ovaries during the long period of disease had become deprived of reactive tissue. Treatment of this patient with estrogen was accompanied by partial improvement. In the 2 male patients it has proved necessary to continue the treatment with a maintenance dose. The treatment is not really substitution therapy, as the preparation used is a chorionic gonadotropin, but it seems to replace the lacking gonadotropic hormone. Chorionic gonadotropin also appears promising for related conditions (pituitary tumors and hypopituitarism), which recently have been called intractable.

J. A. M. A.

Cerebrospinal Fluid

THE CEREBROSPINAL FLUID TOTAL PROTEIN IN THE ALCOHOLIC PSYCHOPATHIES. S. ROSEN, Am. J. M. Sc. **201**:270 (Feb.) 1941.

Rosen undertook to determine whether the total protein content of the cerebrospinal fluid in cases of alcoholic psychopathy was increased consistently enough to be of statistical significance. The study was made on 102 cases of alcoholism. In 42 cases the average total protein content was 31.9 mg. per hundred cubic centimeters, with values ranging from 14.1 to 40 mg. per hundred cubic centimeters. For 60 cases the average total protein content was 58.6 mg. per hundred cubic centimeters, with values ranging from 40.3 to 118 mg. In 43 cases (71.6 per cent) of the latter group and in 10 cases (24.2 per cent) of the former group definite direct or indirect complications of alcoholism referable to the central nervous system occurred. The cytologic changes in the cerebrospinal fluid were not significant, leukocyte counts over 10 cells per cubic millimeter occurring in only 8 cases. The author does not believe that a constant relation to the protein content can be demonstrated for all forms of disease of the central nervous system. He suggests that the alcoholic psychopathies are closely associated with the direct toxic effect of alcohol on the central nervous system and that this action frequently results in the pathologic increase of the total protein in the cerebrospinal fluid.

MICHAELS, Boston.

DETERMINATION OF EFFECT OF PHOSPHATASE IN THE CEREBROSPINAL FLUID. O. SEUBERLING, Deutsche Ztschr. f. Nervenh. **151**:220, 1940.

Phosphatases are ferments which are able to change organic compounds of phosphorus into inorganic compounds. Seuberling describes in detail a method for the determination of the total phosphatase content of the cerebrospinal fluid. Its action is determined by adding spinal fluid in a certain proportion to a standard solution of organic phosphorus. On one half of this mixture immediate determination of inorganic phosphorus is made. The other part of the mixture is incubated before examination. The difference between the two amounts of phosphorus found reveals the inorganic phosphorus which was liberated by fermentation. This difference is directly related to the amount of the phosphatases in the cerebrospinal fluid or to the action of these phosphatases.

ADLER, Boston.

Treatment, Neurosurgery

THE EXPERIMENTAL EFFECT OF SEX-HORMONE THERAPY UPON ANXIETY IN HOMOSEXUAL TYPES. G. DE M. RUDOLF, Brit. J. M. Psychol. **18**:317, 1941.

Chorionic gonadotropin (antuitrin S) was administered to 4 homosexual patients, 2 men and 2 women, who were suffering from anxiety. One was given testosterone propionate (testoviron) later. All the patients had had varying periods of psychotherapy, with small success. Marked improvement of the anxiety occurred during the administration of six to thirteen injections of chorionic gonadotropin over varying lengths of time. A similar result occurred in 1 man who was given two courses of testosterone propionate, of seven doses each. There was some change in those secondary sex characteristics which had shown some abnormality. The anxiety returned at periods of from a few days to four months after the cessation of treatment. The author concludes on the basis of this experience that anxiety in predominantly homosexual patients may be directly dependent on deficiency of "sex hormone."

ALLEN, Philadelphia.

COMPARISON OF THE TOXICITY OF TRYPARSAMIDE AND NEOCRYL IN THE TREATMENT OF NEUROSYPHILIS. A. O. F. ROSS, Brit. M. J. **2**:283 (Aug. 31) 1940.

In 570 unselected cases of neurosyphilis encountered during a three year period, intravenous injections of tryparsamide or neocryl (sodium succinanilomethylamide-paraarsonate), or occasionally of both, in a weekly dosage of 3 Gm. for ten weeks were given. A study of the cases one year after treatment indicated that both drugs gave similar therapeutic results but that neocryl was less often followed by toxic manifestations than was tryparsamide. Of 256 cases in which tryparsamide was used, toxic reactions were manifested in 78, whereas in only 27 of 314 cases in which neocryl was employed were toxic symptoms complained of. Jaundice, dermatitis, neuritis, albuminuria, etc., were noted in many cases after the administration of either drug. Whereas visual disturbances occurred in 47 of the 78 cases in which toxic reactions followed treatment with tryparsamide, only 1 case of visual damage was noted after neocryl therapy. Glyn-Hughes reported similar observations in a study of 77 cases of neurosyphilis. Ross therefore concludes that of the two compounds, neocryl is preferable in the treatment of neurosyphilis because it is less toxic and relatively innocuous to the optic nerve.

ECHOLS, New Orleans.

INSULIN TREATMENT OF SCHIZOPHRENIA IN WARTIME. J. S. MCGREGOR and R. A. SANDISON, Brit. M. J. **2**:310 (Sept. 7) 1940.

McGregor and Sandison describe a method of insulin treatment for schizophrenia in which the amount of sugar required is materially reduced. This became necessary when sugar was rationed as a wartime measure. The method consists

of the intravenous administration of 20 cc. of a 33 per cent solution of dextrose to terminate the coma, followed by the ingestion of a pint (473 cc.) of potato soup, prepared by mixing milk with boiled mashed potato. In the evening ½ pint (237 cc.) of potato soup is given instead of the sweetened drink. McGregor and Sandison terminated 301 comas in this way. It was also found that the injection of insulin intravenously instead of intramuscularly saved on an average 46.6 per cent of insulin. No ill effects followed the intravenous injections, although some investigators have suggested that intramuscular injections are safer. The authors were unable to demonstrate any advantage of protamine zinc insulin over ordinary insulin.

ECHOLS, New Orleans.

THE POSSIBILITIES OF NERVE GRAFTING. F. H. BENTLEY and MARGARET HILL, Brit. M. J. **2**:352 (Sept. 14) 1940.

Bentley and Hill reinvestigated the subject of homeografts. In 8 monkeys, 3 inches (7.6 cm.) of the external popliteal division of the sciatic nerve in the upper part of the thigh was removed and the gap bridged by transplantation of a similar length of the external popliteal nerve from the thigh of another monkey. The extent of regeneration was determined by electrical reactions and histologic examination. A satisfactory motor response of the extensor muscles of the foot was obtained in five hundred days. The authors recommend that gaps in large nerves in man be bridged with grafts from fresh cadavers.

ECHOLS, New Orleans.

TESTOSTERONE PROPIONATE IN FUNCTIONAL IMPOTENCE. A. W. SPENCE, Brit. M. J. **2**:411 (Sept. 28) 1940.

Because testosterone propionate has been beneficial in treating impotence in castrated or hypogonadal patients, its use in the management of functional disturbances has been advocated by some writers. Spence reports on 6 patients with functional impotence probably of psychologic origin who had been treated with intramuscular injections of testosterone propionate in doses varying from 50 to 100 mg. three times a week for from two to six weeks without satisfactory results. He describes the case of another patient with hypogonadism and a psychologic disturbance who also failed to respond to this treatment. However, several observers have reported good results with the administration of the drug. Spence believes that testosterone propionate has no effect on impotence due to psychologic disturbances.

ECHOLS, New Orleans.

CEREBROSPINAL FEVER: ANALYSIS OF ONE HUNDRED AND TWENTY-FOUR CASES. R. W. CUSHING, Brit. M. J. **2**:439 (Oct. 5) 1940.

Cushing reports a detailed analysis of 124 cases of cerebrospinal fever treated with sulfanilamide and its derivatives, given by all routes. In 28 cases the condition was classified as slight, in 49 as moderate and in 41 as severe in intensity and in 6 as of the fulminating septicemic type. Prominent symptoms included intolerable headache, nuchal rigidity, vomiting and cerebral irritation or mental depression. Within twelve to twenty-four hours after the initial injection of soluseptasine (disodium p-(γ-phenylpropylamino)-benzenesulfonamide-α-γ-disulfonate) the patient showed remarkable improvement, at which time sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was given orally. Within eight to nine days treatment was discontinued; the patient was permitted up in from two to three weeks and was discharged four to five weeks after admission. Prior to the use of sulfanilamide and its derivatives, the duration of disability was more than twice as long. Similarly, the mortality rate has been drastically reduced with the advent of these drugs. Whereas the death rate was previously 30 to 60 per cent, in Cushing's series it was 3.2 per cent of 124 cases.

ECHOLS, New Orleans.

CONVULSIVE CARDIAZOL [METRAZOL] THERAPY IN CARDIOVASCULAR DISORDERS. R. GOOD, Brit. M. J. **2**:624 (Nov. 9) 1940.

Good previously demonstrated that convulsive metrazol therapy may result in the temporary appearance after the convulsion of cardiac abnormalities due to exhaustion and anoxemia of the heart muscle. However, he does not believe that a history of cardiovascular disease is a contraindication to the use of convulsive metrazol therapy in cases of mental disease and reports 6 cases to support this view.

ECHOLS, New Orleans.

TREATMENT OF OUT-PATIENTS BY ELECTRICAL CONVULSANT THERAPY WITH A PORTABLE APPARATUS. E. B. STRAUSS and A. MACPHAIL, Brit. M. J. **2**:779 (Dec. 7) 1940.

Strauss and MacPhail describe in detail a cheap, compact portable apparatus which they constructed for electrical induction of convulsions in treatment of out-patients. They have used this apparatus in treating 18 patients in the early stages of various types of mental disorder. The patient does not undress for the treatment and is able to return home after a brief rest. One or two convulsions are produced each week. With few exceptions, their results have been encouraging.

ECHOLS, New Orleans.

BROMIDE THERAPY AND INTOXICATION. FRANCIS PILKINGTON, Brit. M. J. **1**:10 (Jan. 4) 1941.

Pilkington states that the bromide salts are the drugs most widely used in treating nervous conditions characterized by anxiety. In administering this drug, the author emphasizes the importance of finding the optimum dose for each patient. The patient should be under careful clinical observation and should, in addition, be treated with psychologic understanding. The initial dose is from 10 to 20 grains (0.65 to 1.3 Gm.) three times a day. At the end of a week, if there is no improvement, the dose may be increased by about 50 per cent, but should not exceed 90 grains (5.85 Gm.) daily. Mild symptoms of intoxication should be looked for at the end of two weeks. Intoxication from bromides can be prevented by an increased consumption of sodium chloride. This measure is based on the fact that bromides act by replacing the chlorides in the body. Bromide intoxication, should it occur, is treated by immediately stopping the intake of the drug, administering large quantities of bland fluids and giving 30 grains (1.95 Gm.) of sodium chloride every four hours.

ECHOLS, New Orleans.

CHANGES IN TREATMENT AND ESTIMATION OF VERTEBRAL FRACTURES. L. BÖHLER, Arch. f. klin. Chir. **200**:281 (Oct. 18) 1940.

Böhler demonstrated in 1930 that by the reduction of vertebral fractures the lumen of the vertebral canal and the vertebral foramens can be restored and that in this manner the paralysis is avoided in all cases in which the continuity of the cord has not been interrupted. Many observers have reported good results from this method. It is superior to laminectomy because it is less complicated and involves no danger of infection. Böhler made careful studies on more than 60 cadavers in which vertebral fractures had caused paralysis. He observed the effects of longitudinal extension, ventral suspension and dorsal suspension. Böhler classifies cases of vertebral fractures as follows: 1. Cases in which there is no deviation and the paralysis is due to concussion, hemorrhage or edema. In these cases the paralysis disappears spontaneously. 2. Cases in which there is pronounced anterior dislocation of the cranial fragment and the vertebral arch is preserved. In these cases the spinal cord is crushed and reduction, like any other treatment, is without avail. 3. Cases in which there is unilateral or bilateral fracture of the

arch in the interarticular portion. In these cases there exists usually only compression, not severance, of the cord, and the fracture is suitable for nonsurgical reduction. 4. Cases in which there are comparatively slight dislocation and hooking of the articular processes and the spinal cord is usually preserved. These fractures can be reduced in ventral or dorsal suspension after previous partial resection of the articular processes. With regard to vertebral fractures without paralysis, Böhler states that before 1929 he applied a plaster bed in hyperextension and gradually reduced the gibbus, as in cases of spondylitis. A report by Davis, an American author, convinced him that immediate reduction is preferable. Böhler employs reduction and subsequent fixation in a plaster cast, but instead of keeping patients in bed with a cast he lets them up and makes them do gymnastic exercises to avoid muscular atrophy. The treatment embodies the same three principles of reduction, fixation and exercise that govern the treatment of fractures of bone in general. To Magnus' objection that the vertebral body may later collapse and that the length of time the cast has to remain in place is a disadvantage, Böhler replies that for fractures without paralysis the immobilization requires an average of less than four months and for fractures with paralysis an average of six months. Breaking down of the vertebra does not occur if the reduction was complete and was done within the first few days after the accident. It may occur if the reduction was done late or if the fixation was of insufficient duration. To Magnus' charge that the method is expensive, time consuming and annoying to the patient, Böhler replies that reduction is done on the first day and that the patients are up and exercising on the second day. Patients in whom the fracture is not complicated by paralysis and whose occupation does not involve hard physical labor can leave the hospital after seven days and resume their work during the second week. After six weeks, when patients treated by the method of Magnus begin to walk with the aid of supports, Böhler's patients already carry weights of from 20 to 40 Kg. on their heads. Unreduced vertebral fractures are generally extremely painful for a number of days, whereas when the fracture is reduced the patient is free from pain provided the reduction is complete and the plaster jacket fits well. The exercises create self confidence and pride in performance. This can be attested by thousands of physicians who have visited Böhler's clinic and have observed the patients.

J. A. M. A.

FUNCTIONAL TREATMENT OF VERTEBRAL FRACTURES OR BÖHLER'S REDUCTION. H. BURKLE-DE LA CAMP, Arch. f. klin. Chir. **200**:321 (Oct. 18) 1940.

Burkle-de la Camp discusses the relative merits of the Böhler treatment of vertebral fractures by reduction, fixation in plaster and exercises and the functional treatment defended chiefly by Magnus. In the functional treatment the patient is kept recumbent on a thin mattress under which a board is placed. Sandbags are used to effect a gradual reduction of the hump if the gibbus is considerable. During the first two weeks the patient lies on his back but is permitted to lie on a side for short periods. Heat is applied by means of a heating pad. From the third week on heat is applied with the patient in the prone position, and the musculature of the back, excluding the region of the fracture, is massaged. With the beginning of the fifth week the patient is raised to sit up in bed at mealtime; this is gradually increased to a regular exercise. After six weeks the patient gets up and is usually able to bend over without holding the vertebral column stiff. Gymnastic exercises are begun. The patient is able to work after an average of one hundred and thirteen days. In cases of the less severe injuries the time required for treatment is shorter (six or seven weeks). The author analyzes results obtained in a hospital in a mining region, in which during one year 230 fresh vertebral fractures were treated and in which annually from 500 to 600 old vertebral fractures were reexamined. He employed the technic which Böhler has outlined in the latest edition of his book on fractures. He concludes that it is possible to reconstruct a broken vertebra, that such a vertebra will bear loads and that the function of the vertebral column will be completely restored. Some of

these vertebrae, however, will break down in spite of the reduction and sufficiently prolonged fixation. After the reduction treatment there is a greater loss of elasticity than is the case with the functional treatment. The reduction treatment does not produce a more rapid improvement in the paralysis; it may even produce or intensify paralysis, because a bone fragment or a portion of the intervertebral disk may enter the vertebral canal and exert pressure on the cord. The prolonged wearing of a plaster jacket often weakens the patient, besides producing unfavorable psychologic effects. The reduction treatment did not prove advantageous in the author's material. He considers prevention of gibbus formation insufficient justification for Böhler's treatment and considers the functional treatment best.

J. A. M. A.

THERAPEUTIC EFFECTS OF ENCEPHALOGRAPHY ON EPILEPSY IN CHILDREN. I. SCHLEIER, Arch. f. Psychiat. **111**:200 (Jan.) 1940.

Schleier studied the beneficial effect of encephalography in 49 children suffering from epilepsy, all of whom were from 2 to 16 years of age. In all of them the effect was beneficial, as shown by a decrease in frequency of the attacks. It was found that the amount of air injected had no bearing on the effect. The severity of complaints following the injection was directly proportional to the therapeutic effect. The effect was most marked in the younger children and decreased markedly after puberty. It was not dependent on the lapse between the onset of the disease and the time of the encephalographic procedure.

MALAMUD, Worcester, Mass.

Encephalography, Ventriculography, Roentgenography

ROENTGENOLOGIC AND DIFFERENTIAL DIAGNOSIS OF HYPEROSTOSIS FRONTALIS INTERNA. O. Soto, Rev. de neuro-psiquiat. **2**:325 (Sept.) 1939.

The roentgenographic picture of Stewart-Morel disease is characterized by thickening of the calvarium in the vertical portion of the frontal bone which does not reach the orbital plate but may extend backward as far as the parietal region. Hyperostoses involve the inner table of the skull. The inner table loses its parallelism with the outer and encroaches more or less on the intracranial cavity. The degree of thickening may vary considerably. The density of the thickened bone is generally greater than that of normal, and the little areas of osteoporosis visible at some places are not sufficiently marked to change the predominating picture, which is that of osteosclerosis. Frontal views are often valuable in demonstrating the loss of uniform density of this bone and in showing the irregularity in its thickness and the changes in its density. They also show the lateral extension of the hyperostosis and the tendency of the disease to spare the midsagittal line. A uniform thickening of the frontal bone has no diagnostic value.

Differential diagnosis in cases of this condition must take into consideration acromegaly, hemicraniosis, Paget's disease and leontiasis ossea. Osteoma of the vault does not offer great difficulty, since in this condition the outer table ordinarily is involved as well. In cases of acromegaly there is other roentgenographic evidence of the disease and the cranial hyperostoses do not follow the typical distribution found with frontal hyperostosis; furthermore, the inner and the outer table of the skull remain more or less parallel in cases of acromegaly. The differentiation of hemicraniosis depends on the thickening being confined to one half of the skull, usually with involvement of the orbital plate and the region around the gasserian ganglion. Cushing expressed the belief that this disorder was a secondary dystrophy dependent on the existence of a neoplasm of the arachnoid. Furthermore, in this condition there are a decrease in the orbital area and some downward protrusion of the orbital content, with loss of normal roent-

genographic relations with the subjacent maxillary sinus; the frontal sinus on the affected side, as well as the sphenoid and ethmoid cells, show increased density; there are an approximation of the anterior and the posterior clinoid processes and, finally, an increase in density of the superior part of the nasal fossa. There should, then, be little difficulty in differentiating these two conditions. Paget's disease shows a sufficiently typical picture, with alternating areas of osteoporosis and osteosclerosis, together with more widespread distribution and bony changes elsewhere in the body. Leontiais ossea resembles Paget's disease far more than hyperostosis frontalis interna, and in this condition the bones of the face, particularly the superior maxilla, are involved.

NORCROSS, Toledo, Ohio.

THE "NORMAL" PNEUMOENCEPHALOGRAM. H. WOLFF and L. BRINKMANN, Deutsche Ztschr. f. Nervenh. **151**:1 (June) 1940.

Wolff and Brinkmann selected for study as a "normal" group 37 of a total of 966 patients who had had pneumoencephalographic examinations. These 37 patients fell into three diagnostic groups: (1) patients with migraine, (2) patients with minor injuries of the head and (3) patients with "functional" disorders. In each case a standard anteroposterior roentgenogram was made with the head in a strictly vertical position and the tube at a distance of 75 cm. The size of the ventricles and that of an arbitrarily determined area within the skull which was designated as "brain surface" were carefully measured with a planimeter, and a quotient was determined by dividing the latter value by the former. The authors stress precautions that must be observed in order to obtain comparable figures for different patients. Among other things, tipping of the head forward or backward away from the vertical, changing the tube distance or overfilling the ventricles with air all change the desired quotient significantly. Complete figures are given for each case in the series. The authors' figures confirm previous observations that the ventricular system is larger in older patients. They also emphasize the "little known" fact that the size and shape of the ventricular system vary with the size and shape of the skull. There are several excellent figures illustrating the latter point.

BRENNER, Boston.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

JAMES B. AYER, M.D., *Presiding*

Regular Meeting, May 15, 1941

Mechanisms of Headache. DR. HAROLD G. WOLFF, New York.

The sensitivity to pain of the tissues covering the cranium, the cranium itself and most of the intracranial structures has been ascertained from a series of 30 patients during surgical procedures on the head. Some of the "pain pathways" and the mechanisms of headache are defined.

The use of a variety of stimuli has resulted in the following conclusions about the sensitivity to pain of the structures investigated:

1. Of the tissues covering the cranium, all are more or less sensitive to pain, the arteries being especially so.

2. Of the intracranial structures, the great venous sinuses and their venous tributaries from the surface of the brain, parts of the dura at the base, the dural arteries and the cerebral arteries at the base of the brain are sensitive to pain.

3. The cranium (including the diploic and emissary veins), the parenchyma of the brain, most of the dura, most of the pia-arachnoid, the ependymal lining of the ventricles and the choroid plexuses are not sensitive to pain.

With the exception of those sensations that resulted from stimulation of the parenchyma and nerves, pain was the only sensation that was experienced on stimulation of the intracranial structures.

Stimulation of the pain-sensitive intracranial structures on or above the superior surface of the tentorium cerebelli resulted in pain in various regions in front of a line drawn vertically from the ears across the top of the head. The pathways for this pain are contained in the fifth cranial nerve.

Stimulation of the pain-sensitive intracranial structures on or below the inferior surface of the tentorium cerebelli resulted in pain in various regions behind the line just described. The pathways for this pain are contained chiefly in the ninth and tenth cranial nerves and the upper three cervical nerves.

From the data available, six basic mechanisms of headache as regards intracranial structures have been formulated. Headache may result from (1) traction on the veins that pass to the venous sinuses from the surface of the brain and displacement of the great venous sinuses; (2) traction on the middle meningeal arteries; (3) traction on the large arteries at the base of the brain and their main branches; (4) distention and dilatation of intracerebral and extracerebral arteries; (5) inflammation in or about any of the pain-sensitive structures of the head, and (6) direct pressure by tumors on the cranial and cervical nerves containing many pain-afferent fibers from the head.

Intracranial disease commonly causes headache through more than one of these mechanisms and by involvement of more than one pain-sensitive structure. Traction, displacement, distention and inflammation of cranial vascular structures are chiefly resposible for headache.

Headache from intracranial disease is usually referred pain. Local tenderness of the scalp may serve as an index to the structures responsible when a lesion produces direct irritation of pain-sensitive structures. Since disease of remotely separated pain-sensitive structures may cause pain and hyperalgesia in identical areas, the clinical usefulness of such localization is limited. But unilateral hyperalgesia localized in the parietal area indicates the possibility of a lesion near the

middle meningeal artery, and hyperalgesia localized to the postauricular region indicates the possibility of a lesion in the region of the internal auditory meatus.

The association of headache following injection of histamine with increase in the amplitude of the intracranial pulsations was demonstrated photographically. Simultaneous records of the systemic arterial blood pressure, the cerebrospinal fluid pressure, the pulsations of the temporal artery and the intracranial pulsations were made. The demonstrated correlation is taken as further evidence that histamine headache is primarily due to dilatation and stretch of the pial and dural arteries and their surrounding tissues. The extent to which this mechanism affords an explanation for nonexperimental headache is suggested.

Histamine headache does not depend on the integrity of sensation from the superficial tissues. The extracranial and dural arteries play a minor role in contributing to the pain of histamine headache. Cerebral arteries, principally the large arteries at the base of the brain, including the internal carotid, the vertebral and the basilar artery and the proximal segments of their main branches, are chiefly responsible for the quality and intensity of histamine headache. Although there may be other, less important, afferent pathways for the conduction of impulses interpreted as headache after injection of histamine, (*a*) the fifth cranial nerve on each side is the principal afferent pathway for headache resulting from dilatation of the supratentorial cerebral arteries and felt in the frontotemporoparietal region of the head, and (*b*) the upper cervical nerves are the most important afferent pathways for headache resulting from dilatation of arteries of the posterior fossa and felt in the occipital region of the head.

It is likely, for the histamine headache the cerebral branches of the internal carotid, basilar and vertebral arteries at the base of the brain are primarily responsible. To the migraine headache, however, the extracranial, and possibly the dural, branches of the external carotid artery are the chief contributors.

Histamine headache was abolished by increasing the intracranial pressure, thereby giving extramural support to the cerebral arteries at the base of the brain. This is further evidence that histamine headache results mainly from the dilatation and distention of cerebral arteries.

The headache of migraine was not reduced in intensity by increasing intracranial pressure. This is further evidence that such headache arises from extracerebral arteries.

Headache associated with hypertension was not reduced in intensity by increasing intracranial pressure. This is further evidence that such headache has a similar origin in extracerebral arteries.

Scotoma occurring as a preheadache phenomenon of migraine was demonstrated to result from constriction of cerebral arteries. The essential migraine phenomena result from dysfunction of cranial arteries and represent contrasts in vascular mechanisms and vascular beds. Preheadache disturbances follow occlusive vasoconstriction of cerebral arteries, whereas the headache results from dilatation and distention chiefly of branches of the external carotid arteries.

The headache so frequently associated with abnormally high or low cerebrospinal fluid pressures has long been the subject of contradictory speculations. In the study of headache associated with changes in intracranial pressure, the following relevant factors were analyzed. In normal human subjects, headache was induced by drainage of cerebrospinal fluid through a lumbar needle. Observations during studies of headache and manometric changes in spinal fluid during shifts in position on a tilt table were as follows:

1. With the subject erect headaches were regularly induced by removal of 15 to 18 cc. (1 to 2 per cent of total intracraniospinal contents).

2. Such headache responded quickly and directly to changes in the angle of tilt, to jugular compression or to restoration of a normal intracranial fluid volume, measures which altered the amount of traction by the brain on anchoring structures. In these responses the headache was shown to be relatively independent of intracranial pressure.

3. Abnormally high intracranial pressures were produced by intrathecal injection of solution of sodium chloride without headache at any time.

That increased intracranial pressure is not the dominant factor in headache associated with tumor of the brain was suggested by an analysis of 72 cases.

1. Occurrence of headache was almost as common (82 per cent) in 23 cases in which intracranial pressure was not increased as it was (94 per cent) in 49 cases in which pressure was increased.

2. Excluding midline tumors, headache when unilateral was usually (in 83 per cent) on the same side as the tumor.

3. The reduction of elevated pressure did not inevitably eliminate headache due to tumor.

4. At operation the headache could be reproduced experimentally by distortion of pain-sensitive structures adjacent to the tumor.

From these data it is concluded that headache associated with altered intracranial pressure, whether the pressure is high or low, involves the same primary mechanism, namely, traction on pain-sensitive intracranial structures, and that generalized increase or decrease in pressure is merely a contributory, rather than an essential or sole, factor.

DISCUSSION

DR. T. J. C. VON STORCH, Albany, N. Y.: Has Dr. Wolff any evidence that vasoconstriction can cause pain in any part of the body? Most observations concerning the production of pain by vasoconstriction seem to be inferential.

There are several points concerning headache to which I should like to call attention. Masserman has shown that pain follows rapid removal of large amounts of fluid. Cell counts of the fluid after such a procedure have shown that there is a significant pleocytosis. This is indirect evidence that rapid removal of spinal fluid causes active vasodilatation with exudation of cells. I have repeated these experiments and have found the results to be accurate. Thus these observations agree also with Dr. Wolff's.

In a large series of unselected cases analyzed at the Boston City Hospital in the past five years certain observations are worthy of repetition. Among 163 women whose histories were carefully reviewed for evidence of endocrine disorder, Dr. Price and I ascertained that in only 10 per cent was the headache definitely related to the female endocrine cycle. In the others it was largely coincidental. As has been said before, whatever happens to a woman during her menstrual life happens before, after or between her periods. An analysis of the literature by ten different allergists showed that the headache in 661 of 862 cases was significantly allergic in character. On treatment, however, only 25 per cent of patients secured complete relief and not more than 56 per cent obtained any degree of relief, from their migraine through treatment for allergy. Thus another small group may be separated from the total number of those suffering from migraine. Dr. Alvarez, of the Mayo Clinic, has gently, but forcibly, disproved the theory of the gastrointestinal origin of migraine. He has shown that damage to the liver protects one from migraine if it has any effect whatever. In my opinion, intestinal disturbances are largely overemphasized as an etiologic factor.

Recently, in another clinic, the theory of hypovitaminosis has been advanced. Some 60 patients were treated with vitamin B_1 and vitamin B complex, with 65 per cent relief. On the other hand, only 60 per cent of these patients were relieved by gynergen. I do not hold that gynergen is a therapeutic test for migraine, but in a recent analysis I found that in 90 per cent of over 600 cases relief was obtained by administration of this substance. Thus some doubt is cast on the diagnosis in these cases in which vitamin therapy was successful. In fact, the diagnosis of migraine is very difficult. I feel it worth while for those who are working in this field to tabulate the diagnostic criteria of migraine, so that when a physician in Kansas obtains relief with one medicine and another

in Florida with a second, they may both know that they are working with the same disorder. An analysis of these diagnostic criteria by Dr. M. E. O'Sullivan, in New York, is in essential agreement with a similar analysis made by Dr. Maddock and myself.

The vasomotor dysfunction which has been outlined by Dr. Wolff offers an excellent basis for further investigation. One aspect of this research will, I believe, be in the field of carbohydrate metabolism, which is intimately related to the fluid balance, the vitamins and the endocrines.

DR. JOHN R. GRAHAM: I have had experience with 6 cases in which my associates and I ligated the temporal arteries. All of the patients had intractable and persistent headache, whether migraine or not it is difficult to say. Certainly, parts of the histories suggested migraine. In the case of a boy, pressing on the temporal artery gave complete relief from pain. Procaine hydrochloride, injected near the temporal artery, in front of the ear, also relieved him of pain. Ligation of the artery has given relief from pain for six months. It is interesting to hear from Dr. Wolff that some patients have had temporary relief and then there has been return of the headache. I am anxious to hear Dr. Wolff's comments about this. I should be interested to know whether the return of headache is due to a rich anastomosis of cranial circulation. Another patient's headaches were relieved for two or three months, and then there was return to the previous frequency of attacks. In 2 more patients there was no effect. In 1 patient the effect was doubtful. It is interesting to consider whether ligation of something more than the temporal artery would be successful. But this method should be approached only when absolutely all others have failed, and then no guarantees should be given that the operation will be successful.

I agree with Dr. von Storch that Dr. Wolff has demonstrated what might be called a final path of headache and that the problem before the clinician is that of the more remote cause which stimulates that pain pathway to action. The causes may be multiple. It is interesting, in observing several patients who have headache on one side only, to see the effect of small amounts of histamine (given intravenously or subcutaneously). Whereas in most normal people bilateral and universal headache develops after injection of histamine, subjects who have unilateral headache tend to have the histamine headache most prominently on the affected side. A great deal more pain develops on the pathologic side than on the normal side, and in some instances histamine headache develops only on the side on which headache usually occurs. This makes me wonder whether there is a difference in the artery in question on this side which makes it respond to a vasodilating agent in a more dramatic manner. I should like to know whether Dr. Wolff has been able to obtain any pathologic specimens of arteries which have been ligated. I know of one which was found to be normal as far as one could see.

I might also add to Dr. Wolff's remarks on the effect of amyl nitrite on scotoma. I have asked several physicians with typical migraine accompanied by severe scotoma to take some glyceryl trinitrate. Each reported different results. 1. The first subject found that the scotoma became much worse and blinded him. 2. The second experienced no effect at all. 3. The third noted the scotoma grew much less for a few minutes. I assume that this result has to do with the effect of glyceryl trinitrate on the systemic blood pressure. If the systemic blood pressure falls far enough scotoma might be made worse, whereas if the systemic blood pressure does not fall appreciably but local dilatation is increased scotoma might improve. I should like to ask Dr. Wolff if he thinks that vasoconstriction produces the preheadache phenomena and that this is followed by subsequent vasodilatation, which causes headache. Freeman shut off the blood flow in the arm by a tourniquet, and when the tourniquet was released he noted a subsequent increase in blood flow which adequately made up for the total loss during the time the tourniquet was on. I wonder whether one could draw an analogy to the situation in the brain during an attack of migraine.

Dr. Wolff's work is a great relief to those who have been reading books on headache. Headaches are usually classified as those due to such conditions as gastric, uterine and allergic disorders, but until now no one has put his finger on the source of the pain, a contribution which is certainly the first step in approaching the whole problem.

DR. WILLIAM G. LENNOX: Throughout medical history physicians have speculated about the cause of headache, but no audience has heard such a complete exposition of the mechanism of pain as the one presented tonight. However, instead of eulogizing Dr. Wolff's past labors, I should like to encourage him to further work by confronting him with a battery of questions.

Why does one have headache? What purpose is served? Why does pain occur in the head instead of elsewhere? Is the reason anatomic, or is it chemical? Why do some migrainous patients have attacks not of head pain but of abdominal pain? Do animals suffer headache? Are their intracranial structures as sensitive to painful stimuli as those of man?

It is known that heredity plays a part in migraine headache. Does "constitution" also bear the responsibility for the freedom from any sort of headache which some fortunate persons experience? Do persons predisposed to headache possess arteries which respond to stimuli in a peculiar manner, are their sensory nerves different in structure, or do they have a low threshold for pain, but not for other types of stimuli?

Many of Dr. Wolff's observations are based on headache artificially induced by histamine, the mechanism of which may differ from that of spontaneous headache. Histamine headache is a throbbing headache synchronous with the heart beat—clearly associated with the amplitude of pulsation of arteries. Most patients do not have throbbing headache. Histamine causes dilatation of arterioles both inside and outside the head, but so does the inhalation of carbon dioxide, which does not cause pain. Dr. Wolff complicates the problem by supposing dilatation of vessels outside the cranium, which accounts for the pain, and constriction of vessels inside the brain, which accounts for visual disturbances. Is there any evidence that the response of intracranial vessels to chemical stimulation differs from the response of extracranial vessels?

Dr. Wolff and I were the first to demonstrate that the inhalation of carbon dioxide causes dilatation of pial vessels; I wonder why he did not use this substance instead of amyl nitrite as a means of clearing up visual disturbances. The action of carbon dioxide is more sustained and more physiologic.

Finally, Dr. Wolff has dealt for the most part with outlying nerve structures. The twig of the tree is not as important as the root. An attack of migraine is not simply pain in the head but is nausea, malaise, chilliness, perhaps paresthesias or fainting. As Dr. Wolff has shown clearly in his chapter on migraine in Barr's "Modern Medical Therapy in General Practice" (Baltimore, Williams & Wilkins Company, 1940), the person subject to migraine has a characteristic personality. A full understanding of headache necessitates a better understanding of the physiology of the brain and the relation of cerebral function to the chemistry of the body, particularly to the activity of endocrine glands. It is to be hoped that Dr. Wolff can come again and enlighten the members of this society on these points.

DR. HAROLD G. WOLFF, New York: Dr. von Storch has made an important contribution this evening to the discussion of headache. He has shown that headache resulting from injection of air in encephalography is not dependent on changes in pressure, nor is it dependent on the amount of air, but, again, it results from the displacement of pain-sensitive structures.

As to Dr. von Storch's question: Is pain ever due to vasoconstriction per se? I do not know of any instance in which pain resulted from vasoconstriction alone, although it is often associated with vasoconstriction. Much evidence points to the ischemia of parts supplied by a constricted vessel as a source of pain, but I do not believe this indicates that the vasoconstriction is the direct cause of pain.

As far as the head is concerned, vasoconstriction resulting from the application of epinephrine to the arteries does not cause pain. But this experiment, also, does not fully answer the question.

In answer to Dr. Graham's question: My co-workers and I have found no significant histologic changes in the structure of arteries in patients with migraine.

I suggest that the migraine syndrome is characterized by initial vasoconstriction both inside and outside the cranium, with most of the pain coming from dilatation of the vessels outside the cranium.

I do not know what role histamine plays in the migraine syndrome. It is clear, however, that a vessel that is already partly relaxed and dilated, as occurs during an attack of migraine, will respond more quickly and with smaller amounts of histamine than will another vessel.

Dr. Lennox's questions are fundamental and philosophic. I, too, have often asked myself, "Why does one have headache?"

We have done experiments on cats; they, too, act as though they had pain when arteries at the base of the brain are stimulated electrically. I have seen no convincing evidence that histamine headache has clinical significance or that it has any bearing on headaches as they are commonly seen. However, histamine is a very useful tool for producing headache experimentally.

Carbon dioxide is in the same category as histamine, amyl nitrite and a group of agents producing vasodilator effects on cerebral vasculature. Carbon dioxide produces cerebral vasodilatation, with sensations of fulness in the head closely akin to headache, but its dilator effect is not as sudden, as extreme or as prolonged as that of amyl nitrite. The suggestion that we use carbon dioxide in overcoming the visual disturbances that precede headache is an excellent one. The only reason we have not done so is the fact that amyl nitrite is more convenient to have on hand and its administration is simple. Dr. Lennox's questions encompass wide opportunities for work in the future.

DR. AUGUSTUS ROSE: I am interested in the mechanism of the headache. In the case which Dr. Wolff cited, in which the posterior root of the fifth nerve was cut, one was led to believe that headache was relieved because there was no pain in the root. The actual pathway of pain is through the fifth nerve. Does such a conclusion necessarily follow? Dr. Weiss showed that visceral pain is relieved considerably by procainization of the surface. Is it not possible that the actual route of the fibers carrying pain, in this instance, is by way of the sympathetic trunk and that section of the posterior root of the fifth nerve blocks the impulses coming from the region where the pain is experienced by the patient?

DR. HAROLD G. WOLFF, New York: We have not been able to alter the intensity of histamine headache by procainization. We have had no experience with this procedure in other areas of the body. In 12 instances of histamine headache superficial procainization on one side of the head from ear to vertex and from vertex to eyebrows produced no effect on the intensity of the headache. Further evidence that the afferent pathway is the fifth nerve comes from Penfield, who has shown that the dura above the tentorium is insensitive after section of the fifth nerve.

DR. JAMES C. WHITE, Boston: I remember a physician with migraine who asked me if I would try blocking his cervicothoracic ganglia with procaine. As a result of paralysis produced during an attack his headache became worse and pulsating. This fits in with Dr. Wolff's theory and shows that the cervical sympathetic fibers have nothing to do with the conduction of this type of pain.

DR. HAROLD G. WOLFF, New York: We have had opportunities to study histamine headache in patients who have had sympathetic ganglia removed and have found their headaches were not different from histamine headache in subjects with an intact sympathetic chain. Dr. White's suggestion, however, is important, since it is conceivable that efferent sympathetic fibers may have something to do with migraine headache in the sense that constrictive fibers are no longer operating, resulting in painful vasodilatation.

Dr. Theodore J. C. von Storch, Albany, N. Y.: With regard to histamine headache, my associates and I have done some experiments along this line, and we are surprised to hear that the histamine caused localized pain. We used three groups of patients—a group who claimed never to have had headache, another suffering from nonmigraine headaches and a third having characteristic migraine headache. With minute amounts of histamine per body weight, we were unable to produce headache in those not subject to headache. Histamine did, however, produce headache in the other two groups. The pain had no localized character in patients with migraine type of headache but was, however, described as similar.

I should like to ask Dr. Wolff whether he has any observations concerning post-lumbar-puncture headache?

Dr. Harold G. Wolff, New York: Do you agree that post-lumbar-puncture headache is probably due to change in position of the intracranial structures, or does it result from changes in pressure?

Dr. Theodore J. C. von Storch, Albany, N. Y.: In the air injection studies we used very small bubbles, so that there was no distortion of the intracranial contents. The resulting headache appeared to be due to direct irritation of the blood vessel walls. Distortion could not have been more than 0.5 cm. at the most. Only the vascular areas were sensitive.

In post-lumbar-puncture reactions there is apparently vasomotor instability, making different persons more or less susceptible to headache. It is significant that in a study of over 2,000 cases, 16.5 per cent of the outpatient patients had post-lumbar-puncture headache. Twenty-five per cent of those admitted to the hospital had similar headaches. It is of special interest that the position of the patient made no difference in the occurrence of the headache. The percentage was the same in one group who stayed in bed after the puncture as it was in another who got up immediately. Lumbar punctures on private patients of the staff, performed with more ritual than on the other groups, produced headache in 44 per cent.

INDEX TO VOLUME 46

The asterisk (*) preceding the page number indicates an original article in the Archives. Subject entries are made for all articles. Author entries are made for original articles and society transactions. Book Reviews, Obituaries and Society Transactions are indexed under these headings in their alphabetical order under the letters B, O and S, respectively.

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CONTENTS